OUTCOMES OF PERIOPERATIVE IMMUNONUTRITION IN PATIENTS WITH ESOPHAGEAL CARCINOMA UNDERGOING SURGERY

A dissertation submitted in partial fulfilment of MS General Surgery (Branch I) examination of the Tamil Nadu Dr. M.G.R. Medical University, Chennai to be held in April 2017.

CERTIFICATE

This is to certify that the dissertation entitled "Outcomes of perioperative immunonutrition in patients with esophageal carcinoma undergoing surgery" is a bonafide original work of Dr. Sourav Manoram Sahu submitted in partial fulfilment of the requirement for MS General Surgery (Branch I) Degree Examination of the Tamil Nadu Dr. M.G.R Medical University, Chennai to be held in April 2017.

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I, Dr. Sourav Manoram Sahu, hereby declare that this dissertation entitled "Outcomes of perioperative immunonutrition in patients with esophageal carcinoma undergoing surgery" is an original work done by me in partial fulfilment of the requirement for MS General Surgery (Branch I) Degree Examination of the Tamil Nadu Dr. M.G.R Medical University, Chennai to be conducted in April 2017.

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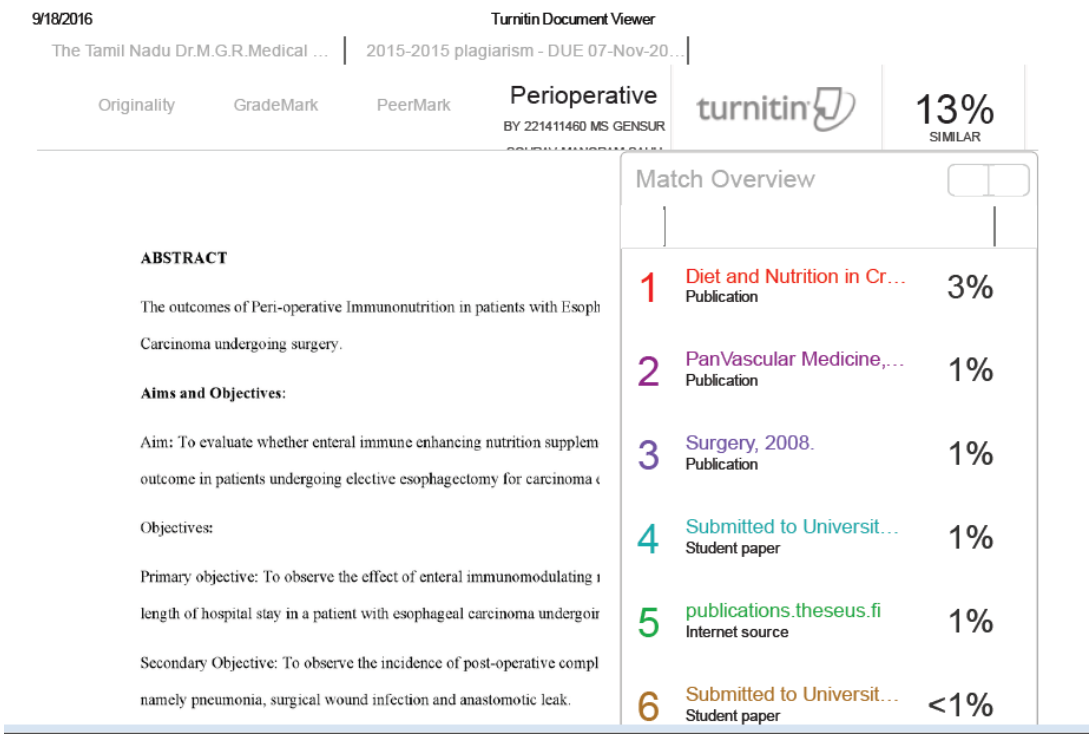
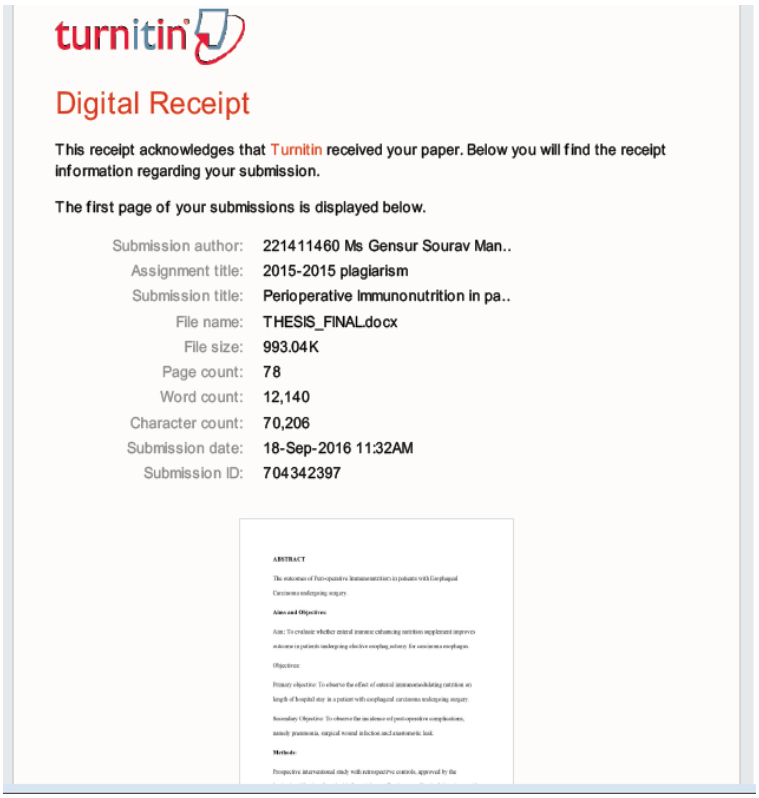
PLAGIARISM CERTIFICATE





ACKNOWLEDGEMENTS

This study could be carried out only due to the untiring efforts and hard work of many individuals. I wish to place in record my sincere appreciation and immense gratitude to them. To my guide, Dr. Vijay Abraham for his continued support and guidance in performing this study.

Ms. Tunny Sebastian; statistician for all her help in the data analysis.

I am immensely thankful to all my patients who consented to be a part of this study and without them study would not have been possible.

My family, friends and colleagues for their love, constant support and encouragement.

I thank GOD for his abundant grace and mercy which is abounding.

ABBREVIATIONS

SCC: Squamous cell carcinoma

AC: Adenocarcinoma

GERD: Gastroesophageal reflux disease

CT: Computed tomography

PET: Positron emission tomography

EUS: Endoscopic ultrasound

SEN: Standard enteral nutrition

EIN: Immune enhancing nutrition

BMI: Body mass index

TLC: Total leucocyte count

N%: Percentage of neutrophils on differential count

L%: Percentage of lymphocytes on differential count

SA: Serum albumin

IMN: Immunonutrition

DHS: Duration of hospital stay

PNEU: Post-operative pneumonia

WI: Post-operative wound infection

AL: Post-operative anastomotic leak

CONTENTS:

ABSTRACT

The outcomes of Peri-operative Immunonutrition in patients with Esophageal Carcinoma undergoing surgery.

Aims and Objectives:

Aim**:** To evaluate whether enteral immune enhancing nutrition supplement improves outcome in patients undergoing elective esophagectomy for carcinoma esophagus.

Objectives**:**

Primary objective: To observe the effect of enteral immunomodulating nutrition on length of hospital stay in a patient with esophageal carcinoma undergoing surgery.

Secondary Objective: To observe the incidence of post-operative complications, namely pneumonia, surgical wound infection and anastomotic leak.

Methods:

Prospective interventional study with retrospective controls, approved by the Institutional Review Board with financial grant for the same. Total of 43 patients with esophageal carcinoma who were planned for elective surgery were included in the study (21 cases and 22 controls). The cases were started on an immune enhancing supplement in form of Glutamine powder at a dose of 0.3g/kg/day four days prior to surgery and were continued on the same post-operatively for a period of two weeks. The total number of days of hospital stay and the incidence of post-operative

complications (pneumonia, wound infection and anastomotic leak) were compared between the two groups.

Results:

43 patients who had esophageal carcinoma and who were planned for elective esophagectomy were studies (21 cases and 22 controls). The cases were patients who underwent elective esophagectomy between April, 2015 and August, 2016. These patients received immune enhancing supplement in form of glutamine. The controls were patient with esophageal carcinoma who underwent elective esophagectomy between January, 2013 and December, 2014. These patients had not received immune enhancing supplements. Statistical test used to compare the total number of days of hospital stay between the two groups was Mann Whitney U test. The p value obtained when comparing the groups of individuals who got immunonutrition and those who did not receive the same was 0.004 which was statistically significant. This meant that the patients who got immunonutrition should stay in the hospital less than those who did not. When we compare the ICU stay of these two groups, there was no significant difference (p=0.295).

The incidence of post-operative pneumonia among the groups were also compared, even if there was difference in proportions(10% v/s 32%), this was not statistically significant (p=0.132). In the case of post-operative wound infection, the groups were not different(p>0.999). Anastomotic leak was less among immunonutrition group, however it was not statistically significant at 5% alpha level. The incidence rates were

compared using Fishers exact test in this study. There were no serious side-effects associated with administration of Glutamine powder.

Conclusion:

Peri-operative Immunonutrition may be safe and effective in reducing the total length of hospital stay in patients with esophageal carcinoma undergoing elective esophagectomy as compared to standard nutrition. However, further large randomized control trials are required to further prove the efficacy of glutamine in patients with esophageal carcinoma undergoing elective surgery.

AIMS AND OBJECTIVES

1) To assess whether enteral immune enhancing nutrition supplement improves the outcome in patients undergoing elective esophagectomy for carcinoma esophagus.

2) Primary objective was to observe the effect of enteral immune enhancing nutrient supplementation on the number of days of hospital stay in patient with esophageal carcinoma undergoing elective esophagectomy.

3) Secondary objective was to observe the incidence of post-operative complications (pneumonia, wound infection and anastomotic leak) in these patients.

JUSTIFICATION

Patients with esophageal cancer, on presentation have poor nutritional status due to mechanical obstruction and cancer related cachexia and hence are at a greater risk of adverse outcomes. Moreover, esophagectomy being a very debilitating surgery puts the patient at greater risk of post-operative complications, further worsening the outcome. Since the early 2000s various randomized controlled trials have shown the beneficial effects of supplementation of immune enhancing nutrients in surgical patients, especially patients with upper digestive tract cancers. All these studies have been done in developed countries and have shown to reduce number of days of hospital stay and incidence of post-operative complications. These have also shown to reduce cost of treatment. Hence this study is specifically designed for patients with esophageal cancer to observe the beneficial effects, if any, of immune enhancing nutrients reported in various studies done in developed countries. Moreover, in a developing country like India, where cost of treatment is a limiting factor, any intervention which can prove to reduce costs can be a boon for the patients. In view of the above stated facts, it is justified to do this study.

LITERATURE REVIEW

ANATOMY

Esophagus is a muscular tube measuring 25-28cms in length extending from the pharynx to the stomach. It extends from the sixth cervical to the eleventh thoracic vertebrae and courses through the neck, thorax and abdomen. It consists of three parts viz:

1. Cervical : It is 5cms in length and extends from the sixth cervical vertebra to the space between the first and second thoracic vertebrae. It is related laterally to the carotid sheath and the thyroid lobes.

2. Thoracic : It is 20cms in length and extends till the diaphragmatic hiatus at the level of the eleventh thoracic vertebra.

3. Abdominal : It is about 2cms in length and ends at the cardia of the stomach.

Esophagus consists of three layers, the mucosa, submucosa and the muscularis propria. The mucosa is lined by stratified squamous epithelium and in distal 1-2cms it transitions to become columnar epithelium. The submucosa has a network of blood vessels and lymphatics. It also contains the Meissner's nerve plexus and mucus glands. The muscular layer consists of a longitudinal outer muscle layer and a circular inner muscle layer. The circular muscle layer is a continuation of the cricopharyngeus muscle. It finally merges with circular muscle layer of the lesser

curvature of stomach. Longitudinal muscle layer arises from the cricoid cartilage and merges with the longitudinal muscle layer of the stomach. Between the two muscle layers, there is a connective tissue layer and nerve plexus called Aurbach plexus. There are striated muscles in the upper third while the distal third consists of smooth muscles. Esophagus lacks a serosal layer which distinguishes it from other parts of the alimentary canal.

There is an outer fibrous layer called adventitia which envelopes the esophagus.

The esophagus consists of three constrictions. The first one is the narrowest

located at the site of the cricopharyngeus muscle and is 1.4cms in diameter. The second is at the tracheal carinal level is due to crossing of the aorta and left main bronchus and is 1.6cms in diameter. The third constriction is located at the diaphragmatic hiatus and is 1.6cms in diameter. In between these constrictions are two areas of dilatations, the superior and inferior dilatation about 2.5cms in diameter. There are two esophageal sphincters, the upper esophageal sphincter and the lower esophageal sphincter. The lower one is characterised by high pressure zones on esophageal manometry but is not easy to recognise anatomically. The upper esophageal sphincter correspond roughly to the cricopharyngeus muscle. The upper esophageal sphincter is in a contracted stateon a normal basis with a mean resting pressure of about 60mm of mercury and the lower esophageal sphincter has a mean resting pressure of 24mm of mercury and prevents reflux.

The esophagus receives its arterial supply from arteries of neck, thorax and

abdomen. The upper cervical part receives branches from inferior thyroid

artery. The cricopharyngeus muscles receives its arterial supply from superior thyroid artery. The throracic part is supplied by four to six esophageal arteries which are direct branches of the thoracic aorta, branches from right and left bronchial arteries, descending branches from inferior thyroid and intercostal arteries and ascending branches of paired inferior phrenic arteries. The abdominal part receives branches from left gastric artery and inferior phrenic artery.

The venous drainage of esophagus starts from the submucosal venous plexuses. The cervical submucous venous plexuses drain to the inferior thyroid vein. The submucous plexuses in the thoracic esophagus drain to superficial venous plexuses and from thence to the azygos and the hemiazygos veins. The abdominal esophagus drains into the systemic venous circulation through right and left inferior phrenic veins and to the portal circulation through left gastric and short gastric veins.

Lymphatic drainage from the esophagus consists of interconnected extensive lymph plexuses in the submucosa which constitute a single plexus. In the proximal two-thirds, lymph flows cephalad while in the distal one-third, it flows caudad.

The nerve supply to esophagus is from both the sympathetic and parasympathetic nerves. The sympathetic nerve supply to the cervical esophagus is from the cervical sympathetic chain which arises from the superior ganglion in the neck and

terminates in the stellate ganglion in the thorax. The thoracic esophagus receives its sympathetic supply from the thoracic sympathetic chain which lie anterior and posterior to the esophagus. Distal thoracic esophagus is supplied by sympathetic fibres from the greater and lesser splanchnic nerves. The abdominal part receives sympathetic supply from the sympathetic fibres around the left gastric artery. Parasympathetic supply to the esophagus is from the vagus nerve via the superior and recurrent laryngeal nerves. They innervate the cricopharyngeus muscle as well as the upper esophageal sphincter. In the thorax, the supply to the striated muscles and the esophageal smooth muscles is from the preganglionic parasympathetic fibres. The sympathetic and parasympathetic fibres form a network around the esophagus and penetrate the esophagus to form the Auerbach's and Meissner's plexus in the intermuscular and the submucosal plane respectively.

PHYSIOLOGY

Transport of materials from the pharynx to the stomach is the major function of esophagus. It also helps in limiting the amount of air that is swallowed as well as the reflux of material in the opposite direction. The design of esophagus is perfect for maintaining these functions. The arrangement of esophageal musculature is optimal for carrying out these functions under non-disease condition. The upper esophageal

sphincter is 4-5cms long and maintains a high resting pressure of about 60 mm of mercury and prevents excess flow of air. The lower esophageal sphincter has a resting pressure of about 24 mm of mercury and prevents gastric contents from refluxing into esophagus. Peristaltic movements of esophagus propels the food forwards caudally. These movements may be primary, secondary or tertiary. Primary peristaltic waves are progressive, generated during voluntary swallowing and move down the esophagus at the rate of 2-4 cm/sec and serve to propel food in the caudal direction. Secondary peristaltic waves are generated due to irritation or distension of esophagus from left over material after passage of primary peristaltic wave. Tertiary peristaltic waves are uncoordinated waves generated by esophageal smooth muscles and are responsible for esophageal spasm. Lower esophageal sphincter relaxation is aided by the peristaltic waves and by vagal stimulation which occurs 1.5 to 2secs after pharyngeal swallowing and lasts for 4 secs, following this the lower esophageal pressure returns to its baseline thereby preventing reflux. The competence of the lower esophageal sphincter depends on the length (atleast 2cms) and pressure (between 6 and 24mm of mercury), radial symmetry and motility of stomach and esophagus. Any defect in the above mentioned factors can lead to the phenomenon of reflux.

HISTORY OF ESOPHAGEAL SURGERY(1)

The history of esophageal surgery is a tale of courageous surgeons who have tried and pioneered their efforts in operating in an uncharted anatomic territory of an organ winding through the posterior mediastinum between major vessels and without a protective covering and marginal blood supply. The first recorded history of esophageal surgery comes from the Smith surgical papyrus which dates back to 2500-3000 B.C. Following its discovery in 1862 many surgeons have tried to perfect the art and science of esophageal surgery. A few honourable mentions are as follows:

1674 : Thomas Willis used whale bone to dilate esophagus (2).

1724: Boerhaave described spontaneous rupture of esophagus.

1844: John Watson performed the first esophagotomy for stricture of esophagus.

1857: Von Middeldorpf performed the first surgery for esophageal tumour.

1868: Kussmaul passes a lighted tube to the stomach through the esophagus.

1872: Billroth performed the first esophagectomy.

1877: Czerny, for the first time, successfully resected carcinoma of cervical esophagus.

1905: Beck described the creation of a gastric tube from the greater curvature of stomach based on gastroepiploic vessels.

1908: Volecker successfully resected carcinoma of gastroesophageal junction with esophagogastric anastomosis using midline laparotomy incision.

1913: Torek successfully resected an esophageal carcinoma using transthoracic approach.

1931: Grey turner performed the first collo-abdominal esophagectomy(2)

1933: Oshawa resected the thoracic esophagus for carcinoma with immediate esophagogastrostomy.

1946: Ivor Lewis performed the first esophagectomy with esophagogastric anastomosis through a right thoracotomy.

1947: Sweet completed 212 esophageal resections.

1963: Logan described 853 esophageal resections for carcinoma esophagus

1978: Orringer and Sloan performed transhiatal esophagectomy (3)

1982: D. Fleischer described endoscopic laser surgery for palliation of esophageal cancer.

1992: Dallemagne described resection of esophageal carcinoma and reconstruction by thoracoscopic and laparoscopic approach (4).

ESOPHAGEAL CARCINOMA

Cancer of Esophagus is the eight most common cancer in the world. It is the sixth leading cause of cancer related deaths (5). The five year survival is around 15-25 % with better survival related to diagnosis of cancer at an earlier stage. Esophageal squamous cell carcinoma(SCC) is the most common histological variant. The global incidence of esophageal carcinoma(SCC) was 5.2 per 100000 (7.7 in men and 2.8 in women) with maximum number of cases in eastern and south-east Asia followed by sub-saharan Africa and central Asia(6). The global incidence of esophageal adenocarcinoma was 0.7 per 100000 (1.1 in men and 0.3 in women) with maximum number of cases in northern and western Europe and northern America. On an individual level, highest rates were seen in the UK and highest number of cases were seen in the US(6). In India, highest number of case of esophageal squamous cell carcinoma are seen in Kashmir valley(7). Males have a higher incidence of esophageal cancer as compared to females(6).

The risk factors for esophageal SCC are as follows:

1. Smoking :The incidence of both squamous cell carcinoma as well as adenocarcinoma is higher in smokers(8). Smokers have a five time higher risk of developing esophageal cancer than non-smokers(9). A study from Taiwan compared smokers and former smokers with non-smokers for the risk of developing esophageal cancer and found that the odds ratio was 4.2 and 3.4 respectively(9). The presence of nitrosamines in smoke condensates on coming in contact with esophageal mucosa and is mainly responsible for causation of cancer.

2. Alcohol: Alcohol ingestion is also associated with increased incidence of esophageal cancer with increase in relative risk depending on volume of alcohol consumed weekly(5). The major carcinogen present in alcohol which is responsible for carcinogenesis is acetaldehyde which under normal circumstances is detoxified in liver by enzyme Glu504Lys. Therefore persons with polymorphisms in this enzyme are more prone to develop esophageal SCC.

2. Chronic Irritation: In conditions like achalasia cardia(10) and esophageal diverticuli due to release of harmful chemicals by bacterial decomposition of accumulated food , there is an increased chance of developing SCC(11). Persons who have consumed acid or similar corrosive fluids have a higher risk for development of esophageal SCC(12).

3. Diet and nutrition: Tea, coffee and other hot beverage consumption increases the risk of developing esophageal squamous cell carcinoma due to direct thermal injury to the esophageal mucosa(13). A diet rich in refined foods and saturated fatty acids increases the risk of developing esophageal carcinoma. Smoked and pickled foods which contain increased amounts of nitrosamines are also found to increase the risk of development of esophageal squamous cell carcinoma whereas a diet rich in fruits and vegetables reduces the risk of the same(14). Consuming betel quid or areca nut is also associated with increased incidence of developing esophageal squamous cell carcinoma(9).

4. Genetics: There is an increased incidence of esophageal squamous cell carcinoma in patient with tylosis which is an autosomal dominant inherited disorder with defect

in chromosome 17q25(15). An increased risk of developing esophageal squamous cell carcinoma is seen in patients with polymorphisms in genes encoding for enzymes alcohol dehydrogenase 1B, aldehyde dehydrogenase 2 and phospholipase C1(16).

5. Others: Patient belonging to low socioeconomic status have an increased risk of developing esophageal SCC(17). Plummer Vinson syndrome also increases the risk of developing esophageal SCC(18).

The risk factors for developing esophageal adenocarcinoma are:

1. Gastroesophageal Reflux Disease: Patients with symptomatic reflux have up to eight times higher risk of developing esophageal adenocarcinoma(19). Drugs relaxing lower esophageal sphincter and hence increasing reflux like aminophylline, anti-cholinergics and beta-blockers increase the incidence of GERD and up to 10 percent of cases occurring in the population can be a attributed to these drugs(20).

2. Obesity: It is a definite risk factor for development of esophageal AC. Studies have shown that body mass index more than 25 is associated with a higher risk of development of esophageal adenocarcinoma (males : OR – 2.2 and females: OR – 2)(21). Obesity causes an increase in intraabdominal pressure and hence reflux. Insulin like growth factors and leptins which are increased in obese persons also play a role in the pathogenesis of esophageal adenocarcinoma(22).

3. Barrett's esophagus: It is a condition in which the normal stratified squamous epithelium of the esophagus is replaced with intestinal epithelium. It is a complication seen in patient with long-standing gastroesophageal reflux. It is seen as a salmon patch of mucosa extending from the gastroesophageal junction into the pale coloured

esophageal mucosa. It occurs in about 5 to 8 percent of patients with GERD(23). Patients with Barrett's esophagus have an annual risk of about 0.12 percent to 0.5 percent for the development of esophageal AC(24).

4. Smoking and alcohol: Smoking is a known risk factor for esophageal adenocarcinoma with increased incidence and aggressiveness of cancer in smokers as compared to non-smokers(25). Alcohol, though a known risk factor for squamous cell carcinoma(SCC) of esophagus, is not a risk factor for adenocarcinoma of esophagus(25). A study by Anderson et al had also shown that alcohol consumption does not increase the incidence of reflux esophagitis, Barrett's esophagus or adenocarcinoma(26).

5. Age and sex: Increasing age and male gender have been found to be risk factors for the development of esophageal adenocarcinoma with males having a six times higher risk for developing adenocarcinoma of esophagus(27).

6. Genetic factors : Studies have shown that presence of aberrant cyclin kinase inhibitor and DNA mismatch repair genes increase the risk of development of esophageal adenocarcinoma(28). Increase expression of p53 gene has also been found to increase the risk of patients with Barrett's esophagus to develop adenocarcinoma of esophagus(29).

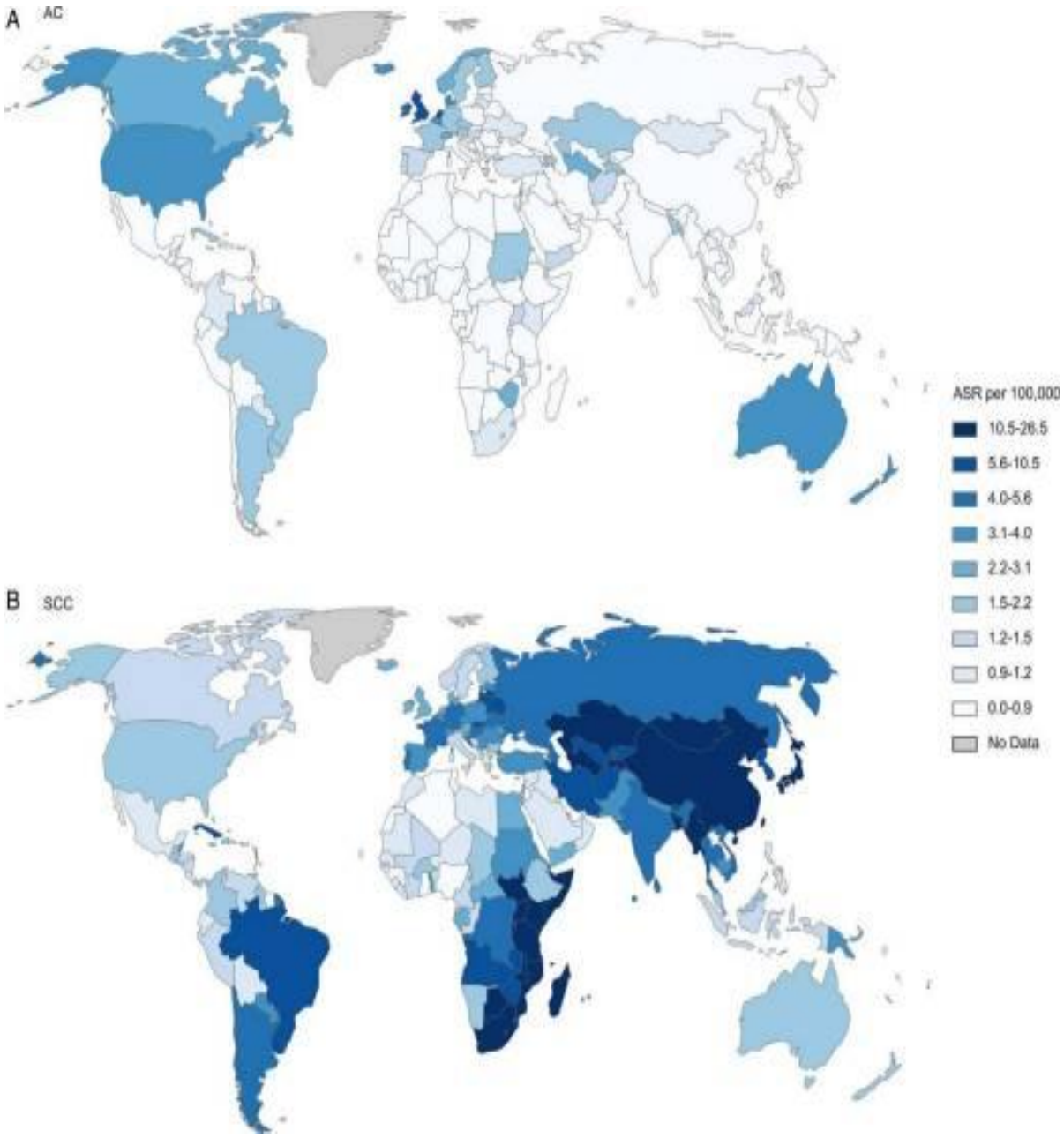
Table 1. Risk Factors for Esophageal Cancer.*

Risk Factor	Squamous-Cell Carcinoma	Adeno-carcinoma
Tobacco use	+++	++
Alcohol use	+++	—
Barrett's esophagus	—	++++
Weekly reflux symptoms	—	+++
Obesity	—	++
Poverty	++	—
Achalasia	+++	—
Caustic injury to the esophagus	++++	—
Nonepidermolytic palmoplantar keratoderma (tylosis)	++++	—
Plummer–Vinson syndrome	++++	—
History of head and neck cancer	++++	—
History of breast cancer treated with radiotherapy	+++	+++
Frequent consumption of extremely hot beverages	+	—
Prior use of beta-blockers, anticholinergic agents, or aminophyllines	—	±

* A single plus sign indicates an increase in the risk by a factor of less than two, two plus signs an increase by a factor of two to four, three plus signs an increase by a factor of more than four to eight, and four plus signs an increase by a factor of more than eight. The plus–minus sign indicates that conflicting results have been reported, and the dashes indicate that there is no proven risk.

Image courtesy: Esophageal Cancer : Enzinger et al. New Engl J Med; December 4,2003

Global distribution of Esophageal Cancer (image source GLOBOCAN-2008)



Pathology:

1. Squamous Cell Carcinoma(SCC) Esophagus: Squamous cell carcinoma most commonly affects middle third of esophagus. It arises as small polypoid excresences, denuded epithelium or plaques. They may also present as circumferential ulcerated or fungating masses. They infiltrate the submucosa at an early stage and extend along the wall of the esophagus(28). Lymphatic invasion occurs at an early stage due to presence of lymphatics in the lamina propria as compared to muscularis propria in the rest of the gastrointestinal tract. Invasion of local structures like trachea or aorta can lead to tracheoesophageal fistula or massive upper gastrointestinal haemorrhage respectively. Distant metastasis occurs to liver, bones and lung in about 30 percent cases.

2. Adenocarcinoma(AC) Esophagus: The majority of cases are located near lower third of esophagus and gastroesophageal junction. It is most commonly associated with previous Barrett's esophagus. Adenocarcinoma arising in Barrett's esophagus may present as a nodule, an ulcer or as an altered mucosal pattern. As with squamous cell carcinoma, early lymph nodal metastasis is seen with involvement of celiac and perihepatic nodes(30).

Clinical features

Patients with esophageal cancer most commonly present with dysphagia(31). It occurs with reduction of diameter of esophageal lumen to below 13mm. The other symptoms being weight loss, gastroesophageal reflux, odynophagia and dyspnea. Some

asymptomatic patients can also be found to have an esophageal carcinoma on routine surveillance endoscopy.

Diagnosis

The various modalities used in diagnosis of cancer of esophagus are barium studies, endoscopy, endoscopic ultrasound, CT scan and positron emission tomography (PET) scan. Double contrast barium study is a very sensitive study for diagnosis of carcinoma of esophagus and that located at gastroesophageal junction with a positive predictive value of 42 percent(32) . It has also been used to estimate the depth of tumour invasion and hence plan for endoscopic mucosal resection of patients with only superficial invasion. The tumours can be seen as polypoidal lesions, infiltrative or ulcerative growths on barium studies. It is also helpful in differentiating between benign and malignant strictures(33). Endoscopy is used for direct visualisation of the tumour and to take biopsy. Endoscopy gives dual advantage of assessment and biopsy. The main use of CT scan and PET scan is for accurate staging of disease and identification of patients who can undergo surgical resection. Thus cross-sectional imaging is mainly used to compliment the information got from barium studies and endoscopy. CT scan cannot identify the layers of the esophagus and hence T1 and T2 lesions cannot be differentiated on CT scan. It can however, give information about invasion of the peri-esophageal fat and mediastinum with a sensitivity ranging from 59 to 82 percent(34). The accuracy in determining regional lymph node and abdominal lymph node spread by CT scan is between 50-70 percent and about 85 percent respectively(34). Endoscopic ultrasound (EUS) can delineate various layers of the esophagus and hence is the most sensitive for knowing the depth of tumor

invasion and local and regional spread of the disease with an accuracy of about 85 to 90 percent(35). It can also help for taking biopsy from suspicious adjacent lymph nodes to get information about lymph nodal metastasis(36). The only drawback of EUS is the inability to assess patients with malignant strictures. CT scan and EUS when used together improve the accuracy of TNM staging up to 86 percent and some studies have recommended using CT scan to determine the presence of distant metastasis followed by EUS to know the extent of locoregional spread(37). Positron emission tomography using 2-F-18 fluoro-2-deoxy-D-glucose(FDG-PET) helps to stage the disease along with CT scan. Overall accuracy for lymph nodal staging ranges from 48 percent to 90 percent(33). PET scan can detect metastasis in distant nodes, liver, lungs, bones, adrenals etc. It can also predict survival rate with a higher FDG uptake associated with lower survival(38).

Staging of Esophageal Cancer

The staging system used universally is TNM staging system developed by American Joint Committee on Cancer (AJCC) and the International Union against Cancer (UICC). Tumors at lower esophagus involving esophagogastric junction, at esophagogastric junction and those that extend into the proximal 5cm of stomach from esophagogastric junction or esophagus are also classified and staged as esophageal cancers(39). The standardised staging system helps to obtain accurate pre-treatment staging and to provide appropriate treatment which is crucial in improving outcomes. It is also helpful in providing accurate prognostic information. The staging as proposed by the 7th edition of AJCC classification is as follows(40).

T, N, and M staging and histologic grade definitions for esophagus and esophagogastric junction cancer is a follows(40)**:**

T status

T_{is}	High-grade dysplasia.
T1	Invasion of lamina propria, muscularis mucosae, or submucosa.
T2	Invasion of muscularis propria.
T3	Invasion of adventitia.
T4a	Invasion of resectable adjacent structures (pleura, pericardium, diaphragm).
T4b	Invasion of unresectable adjacent structures (aorta, vertebral body, trachea).

N status

N0	No regional lymph node metastases.
N1	1 to 2 regional lymph nodes positive.
N2	3 to 6 regional lymph nodes positive.
N3	7 or more regional lymph nodes positive.

M status

M0	Distant metastases absent.
M1	Distant metastases present.

Histologic grade

G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

AJCC 7th edition stage groupings(40)

Stage	Adenocarcinoma				Squamous cell carcinoma				
	T	**N**	**M**	**Grade**	**T**	**N**	**M**	**G**	**Location**
0	is	0	0	1	is	0	0	1	Any
IA	1	0	0	1-2	1	0	0	1	Any
IB	1	0	0	3	1	0	0	2-3	Any
	2	0	0	1-2	2-3	0	0	1	Lower
IIA	2	0	0	3	2-3	0	0	1	Upper, middle
					2-3	0	0	2-3	Lower
IIB	3	0	0	Any	2-3	0	0	2-3	Upper, middle
	1-2	1	0	Any	1-2	1	0	Any	Any
IIIA	1-2	2	0	Any	1-2	2	0	Any	Any
	3	1	0	Any	3	1	0	Any	Any
	4a	0	0	Any	4a	0	0	Any	Any
IIIB	3	2	0	Any	3	2	0	Any	Any
IIIC	4a	1-2	0	Any	4a	1-2	0	Any	Any
	4b	Any	0	Any	4b	Any	0	Any	Any
	Any	3	0	Any	Any	3	0	Any	Any
IV	Any	Any	1	Any	Any	Any	1	Any	Any

Location of cancer: Upper thoracic - 20-25cm from the incisors. Middle thoracic - 25-30cm from the incisors. Lower thoracic - 30-40cm from the incisors.

Prognosis

At presentation, more than 50 percent patients have advanced and unresectable disease. The overall 5 year survival has increased from 5 percent earlier to about 17 to 19 percent(41) due to improvement in detection and treatment. Patients with metastatic disease, receiving chemotherapy have a median survival of only about one year. Apart from TNM staging, presence of dysphagia, advanced age, tumour size and presence or absence nodal metastasis on CT scan are independent prognostication features for survival(42). The overall five year survival for patients with esophageal cancers is as follows:

Stage	Tumor	Node	Metastasis	5-Yr Survival %
0	Tis	N0	M0	>95
I	T1	N0	M0	50–80
IIA	T2-3	N0	M0	30–40
IIB	T1-2	N1	M0	10–30
III	T3 T4	N1 Any N	M0 M0	10–15
IVA	Any T	Any N	M1a	<5
IVB	Any T	Any N	M1b	<1

Image courtesy: Prognosis of Carcinoma Esophagus(43)

Treatment of Esophageal cancers

The treatment is tailored according to the stage of presentation of the patient(44). In patients having stage 0 disease, endoscopic treatment in form of endoscopic mucosal resection is enough for curative purposes. Patients presenting with stage I disease, either surgical treatment followed by adjuvant chemoradiotherapy is advised. In patients presenting with stage II disease if there is absence of lymph nodes, then esophagectomy followed by adjuvant therapy is recommended but in presence of lymph node metastasis, neo-adjuvant therapy followed by esophagectomy is preferred. In patients with stage III disease pre-operative chemoradiotherapy followed by esophagectomy is often practised. Patients presenting with unresectable stage IV disease only chemoradiotherapy is advised.

Esophagectomy either Ivor Lewis, Mckeown or transhiatal is a major surgery associated with significant morbidity and mortality(45). The major predictors of mortality and morbidity are age, body mass index, nutritional status, ASA grade, presence or absence of pulmonary disease, hypertension, coronary artery disease and hepatic/renal disease. The major surgical complications seen are anastomotic leak, recurrent laryngeal nerve injury or bleeding. The major general complication is post-operative pneumonia followed by ARDS, myocardial infarction/arrhythmia, renal failure and pulmonary embolism(46).

As already discussed above, esophageal cancer is associated with several factors that lead to a poor nutritional status and this further worsens the prognosis. Chemotherapy and radiation further pre-disposes patients to increased post-operative morbidity,

further worsening the already existing malnutrition(47). Studies have also shown that major surgery(esophagectomy in this case) and trauma is associated with a reduction in cell mediated immunity and hence an increase in the incidence of post-operative complications. Use of immune enhancing diets given prior seem to reduce these complications(48). Hence there is need for immune enhancing supplementation prior to a morbid procedure like esophagectomy.

Immunonutrition

It is the addition of "immune enhancing nutrients" to the diet. These nutrient help to improve the immune system and hence help in improving the post-operative outcome. The major contributors to post-operative morbidity are infectious complications which increase the length of hospital stay as well as increase the cost of treatment(49). Major surgery is usually followed by systemic inflammatory response in which there is increase of polymorphonuclear cells and pro-inflammatory cytokines. This is followed by a phase of compensatory anti-inflammatory response where there is reduction in the circulating lymphocytes which lead to increased susceptibility of post-operative infections and hence morbidity. There is a need to modulate this immune response so that a balance can be maintained between these two phases which will be beneficial to the patient. A recent study done by Kassin et al on the risk factors which lead to increased 30 day admission rates in surgical patients found that the main reasons were gastrointestinal complications, surgical site infection and post-operative malnutrition(50). Post-operative pneumonia was also among the most common causes of readmission. There has been a positive correlation between malnutrition and

increased risk of infection and post-operative morbidity(51). Malnutrition is widely prevalent among patients with esophageal cancer due to dysphagia and odynophagia. Malnutrition along with surgical stress of an esophagectomy leads to depression of immunity and increased post-operative complications and hence morbidity(52). Malnutrition also leads to lymph nodal atrophy, decreased total lymphocyte population and dysfunctional cellular immunity that further leads to increased post-operative complications(53). Hence, it is of prime importance to supplement these surgical patients with appropriate nutritional support to overcome the state of immunosuppression and malnutrition associated with carcinoma of esophagus. Many studies in the past have shown that there is a deficiency of amino acids like arginine and glutamine in the post-operative period(54). This led to the supplementation of arginine in the post-operative period which showed significant reduction in post-operative complications and infection rate(54). This has resulted in the concept of supplementation of immune enhancing nutrients in the diet of post-operative patients. Immunonutrition has been effective in reducing the post-operative infectious complications. It has also led to reduction in length of hospital stay by improvement in cellular immunity, enhanced phagocytic activity of neutrophils and improved T-cell function(55). The supplementation of an immune enhancing diet has been studied extensively in patients undergoing surgery for upper gastrointestinal tract cancers, trauma and patients with critical illness. Most studies have used commercially available formulas containing a mixture of immune enhancing supplements but use of a single immune enhancing agent is seen only in few studies. Earlier studies had also shown that the use of immunonutrition is beneficial only in malnourished patients but

recent studies have shown its beneficial effect in well- nourished individuals as well(56). Peri-operative immunonutrition is clinically significant in many patients undergoing esophagectomy as it leads to improved lymphocyte counts, reduced rates of incisional wound infection and reduced post-operative systemic inflammatory response and hence improvement in post-operative outcome(57). Post-operative pneumonia which is a major complication following esophagectomy has also shown a declining trend with the use of perioperative immunonutrition(58). The various components used in immunonutrition are arginine, glutamine, omega-3 fatty acids and nucleotides. They have been found to modulate post-operative immunosuppression and systemic inflammatory response following major surgeries. The brief mechanism by which these nutrients work are as follows:

1. Arginine: It is a conditionally essential amino acid, synthesized by the human body. The amount produced is optimal for normal physiological function. In conditions of increased metabolic needs like surgery or trauma, the amount produced is not enough to maintain body functions. In conditions of stress arginine acts as a major fuel for T-lymphocytes thereby helping in maintaining the immune system and resulting in reduced risk of infection(59). Studies have shown that arginine helps in maturation of CD3+ T-lymphocytes and in a dose dependent manner helps in proliferation of CD8+ T-lymphocytes(60). It also helps in increasing T-cell receptors on these cell populations on the surface of cells. Thus, arginine may become conditionally essential in times of excess stress. Arginine also acts as a substrate which is used by the enzyme nitric oxide synthetase to produce nitric oxide. Nitric oxide acts as a potent vasodilator improving oxygenation of tissues. It also helps in

enhancing wound healing. Vasodilatation helps in recruitment of polymorphonuclear leucocytes and macrophages. Nitric oxide has also been found to have intrinsic bactericidal action(54). Arginine due to the above stated action should be used cautiously in patients with septic shock as further vasodilatation can be detrimental in this subset of patients(59). Arginine can be metabolised to hydroxyproline by action of enzyme arginase-1. Hydroxyproline has been found to help in connective tissue repair and wound healing(61). Therefore, arginine supplementation in supra-physiological concentration can lead to immunomodulation and improved outcomes following major surgery and trauma.

2. Omega-3 fatty acids: These are long chain polyunsaturated fatty acids which have been found to be beneficial both in modulating the immune system as well as an anti-inflammatory agent. The main omega-3 fatty acids used are eicosapentanoic acid and docosahexanoic acid. Their main function is to decrease the levels of arachidonic acid and to increase production of protectins and resolvins which play a major role in reducing inflammation and enhancing wound healing(62). It was found that omega-3 fatty acids also enhanced the function of immune system.

3. Nucleotides: Nucleotides are building blocks of nucleic acids like ribonucleic and deoxyribonucleic acids. They are essential for rapidly proliferating cells like T-lymphocytes. They also help increase villus height, mucosal proteins and brush border enzymes when supplemented in the diet(63).

4. Glutamine: The role of glutamine as an immunonutrient will be discuseed in greater detail at a later stage since it is the immunonutrient that was used in this study.

Current Evidence on the use of Immunonutrition

Many randomised control trials and their meta-analyses have evaluated the use of Immunonutrition in patients undergoing surgery for malignancy either in pre-operative, peri-operative or post-operative period. Most of the studies, though controversial, have reported a reduction in length of hospital stay as well as a reduction in infectious complications post-operatively.

Suzuki et al(64) studied the effect of immune enhancing nutrition on cell mediated immunity and differentiation of T-helper cells(Th1/Th2) in patients undergoing pancreaticoduodenectomy. He found that the patients receiving peri-operative immunonutrition had improved cell mediated immunity in form of increased T-lymphocyte, natural killer cell activity and levels of messenger RNA of several immune mediators. There was also a decrease in the number of infectious complications in patients who received peri-operative Immunonutrition. Sakurai et al(65) studied the effect of peri-operative Immunonutrition on immunological and metabolic status of patients undergoing esophagectomy found that there was increased proliferation of lymphocytes with a B-cell dominance at third and fifth day after operation, which may be useful in reducing the number of post-operative infectious complications. Numerous trials have studied the use of immune enhancing nutrition in the pre-operative, post-operative or peri-operative(both pre- and post-operative) phases. A few important studies have been discussed below:

1. Pre-operative: In the pre-operative phase, enteral feeding formulas enriched with immunonutrients have been found to improve intestinal microperfusion, gut oxygenation and post-operative immune status(66). It was found that pre-operative Immunonutrition led to reduction in length of hospital stay as well as a reduction in infectious complications post-operatively. There was no change in overall mortality. Braga et al(56) demonstrated that patients who received pre-operative immune enhancing nutrition had a decreased incidence of post-operative complications (12 percent v/s 32 percent) and also had a reduction in length of hospital stay (9.5days v/s 12 days) than patients who received standard enteral feeds. In another study done by Braga et al(67) on the effect of pre-operative Immunonutrition in patient undergoing major gastrointestinal surgeries (it included patients with esophageal, gastric, pancreatic and colorectal cancers) it was found that there was a decrease in post-operative complications as well as length of hospital stay in patients receiving pre-operative Immunonutrition. Gianotti et al(68) also supplemented immune enhancing diet in individuals with gastrointestinal malignancy and found that there was a decrease in infectious complications post-operatively (15.8 percent v/s 30.4 percent) and reduction in total duration of hospital stay (11.7 days v/s 14.0 days) in patients who received immune enhancing diet. There are other studies that have found conflicting results. A study by McCarter et al on pre-operative Immunonutrition in cancer patients showed no change in lymphocyte proliferation or clinical outcome between patients supplemented and not supplemented with immune enhancing diet. Another large prospective study by Fujitani et al(69) on pre-operative Immunonutrition in well- nourished patients with gastric cancer undergoing elective

total gastrectomy found no significant difference in the number of infectious complication or the duration of systemic inflammatory response in patients who received pre-operative immune enhancing diet. Barker et al(70) compared pre-operative Immunonutrition in well-nourished and malnourished patients who underwent surgery for gastrointestinal cancers and found a non-significant reduction in the length of hospital stay in the group receiving pre-operative Immunonutrition with the effect being more pronounced in the malnourished group. In another double blind randomised control trial by Ryan et al(71) 53 patients undergoing esophagectomy, who were randomised to receive pre-operative immune enhancing nutrition or isonitrogenous standard nutrition, it was found to have no difference in the rate of post-operative complications or levels of inflammatory markers. However, the study showed that the group receiving Immunonutrition did not have any loss of weight as compared to the other group.

2. Peri-operative Immunonutrition: There have been many studies which have evaluated the effect of peri-operative Immunonutrition in patients with upper gastrointestinal cancers undergoing surgery. Senkal et al(72) studied the effect of peri-operative immune enhancing nutrition in patients with upper gastrointestinal tract cancers undergoing surgery and found that there was reduction in post-operative infectious complications as well as complications after third post-op day. It was also found that the total duration of hospital stay was less in patients who received peri-operative Immunonutrition. Braga et al(73) randomised 206 patients with gastric, pancreatic and colorectal cancers to receive 7 days of immune enhancing formula or a isonitrogenous feeding formula pre-operatively and then post-operatively (by feeding

jejunostomy or orally). There was a 16 percent reduction in post-operative infectious complications as well as a decrease in the number of days of hospital stay. In another study by Klek et al(74), 305 patient with gastric and pancreatic cancers were randomised to receive immune enhancing nutrition or standard enteral feeds, after being provided with 14 days of parenteral feeds. It was found that the group receiving immune enhancing nutrition had lesser infectious complications (28.3 percent v/s 39.2 percent, p=0.04). The group receiving immune enhancing nutrition also had reduced duration of hospital stay, morbidity and mortality though there was no difference in surgical complications, organ function or tolerance to treatment. The role of peri-operative Immunonutrition has also been studied in patient with non-gastrointestinal cancer patients. Snyderman et al studied the effect of peri-operative Immunonutrition in head and neck cancer patients and found that there was reduced icidence of infectious complications, however, there was no difference in the duration of hospital stay or complications associated with wound healing. Celik et al studied peri-operative Immunonutrition in patients with gynaecological malignancy undergoing operation (2 days pre-operatively and 7 days post-operatively). It was seen that the lymphocyte counts and CRP levels were higher in the immunonutrition group. The number of days of post-operative hospital stay, wound infections and overall complications were much lower in the group receiving immune enhancing nutrition. Finco et al(75) studied the effect of peri-operative immunonutrition in patients undergoing laparoscopic colorectal surgery. Although there was increased CD4+ cell count in patients receiving immune enhancing nutrition, there was no difference in the post-operative infectious complications. Klek et al(76) studied the effect of immune

enhancing nutrition in 214 patients undergoing resection of upper gastrointestinal cancers. It was seen that the patients receiving immune enhancing nutrition and standard nutrition did not differ significantly in terms of overall morbidity, infectious complications and length of hospital stay. There have been other studies which have evaluated the addition of glycine in immune enhancing formula and have found no difference in the post-operative patient outcomes.

3. Post-operative: Immune enhancing diets have also shown to have benefit when used post-operatively. Daly et al(77) randomised 60 patients (22 esophageal, 22 pancreatic and 16 gastric cancer) to receive either immune enhanced feeds or standard feeds (both given by feeding jejunostomy tube from the first post-operative day). It was found that there was an increase in the levels of omega 3 and omega 6 fatty acids and a decrease in levels of prostaglandin E2 levels by post-operative 7^{th} day but no such change was seen in patients receiving standard diet. There was a reduction in post-operative infectious complications (10 percent v/s 43 percent, $p< 0.05$) and mean duration of hospital stay (16 v/s 22 days with $p < 0.05$) in the group receiving immune enhancing nutrition. In another prospective study done by Daly et al on 85 patients undergoing surgery for upper gastrointestinal cancer it was found that patients receiving immune enhancing nutrition had reduced wound and infectious complications (11 percent v/s 37 percent, $p = 0.02$) as well as reduced mean duration of hospital stay (15.8 v/s 20.4 days with $p = 0.01$) than patients receiving standard nutrition. In another study by Marano et al(78) 109 gastric cancer patients were randomised to receive early enteral feeding (within 6 hours of surgery) with either an immune enhancing diet or isonitrogenous standard diet. There was a decrease in post-

operative infectious complications (7.4 percent v/s 20.4 percent, $p < 0.05$) and a reduction in the length of hospital stay which was significant, (12.7 days v/s 15.9 days, $p = 0.029$) in the group receiving immune enhancing nutrition, though the mortality was same in both groups. Studies have also evaluated the role of post-operative immune enhancing nutrition in non-gastrointestinal cancer patients. Casas Rodero et al divided 44 oral and laryngeal cancer patients randomly to receive post-operative immunonutrition or normal enteral nutrition and found that there was similarity in the duration of hospital stay between the two groups but the group receiving immune improving nutrition had reduced post-operative infection. In one of the earlier studies by Braga et al, done in 1996(79) on the effect of post-operative immunonutrition in patients undergoing major abdominal operation, it was found that though the patients who received immune enhancing nutrition recovered their nutritional and immunological status faster, there was no difference in the rate infectious complications post-operatively. In another study by Lobo et al(80), 120 patients with gastric and esophageal cancers were randomised to receive post-operative immune enhancing nutrition or isonitrogenous standard enteral nutrition. It was found that there was no outcome advantage with both groups having similar rates of post-operative complications (infectious) and duration of hospital stay.

Thus, there are numerous studies which have shown Immunonutrition to be advantageous and many others which have shown that it makes no difference to the post-operative outcome. Due to discrepancies in many of the above stated studies, there have been numerous meta-analysis of the randomised control trials on Immunonutrition to know whether or not Immunonutrition alters the post-operative

outcome in surgical oncology patients. Some of the meta-analyses have been discussed below:

1. Zheng et al(81) studied the effect of peri-operative Immunonutrition on the clinical outcome and immune status in patients undergoing surgery for gastrointestinal cancers. They analysed studies which compared perioperative Immunonutrition (with two or more immunonutrients like glutamine, arginine, omega-3 fatty acid or nucleotides) with normal enteral nutrition. A total of 13 randomised control trials with a total of 1269 patients were included out of which six trials were double blinded (627 patients). There were no significant side-effects of Immunonutrition. The rates of infectious post-operative complications as well as the total duration of hospital stay was significantly lower in the peri-operative Immunonutrition group as compared to the group that received standard enteral nutrition. Three of the trials also showed increased T-lymphocyte counts post-operatively. The groups were similar to each other in terms of mortality, CD8, IL-2 and CRP levels. Another meta-analysis of 35 randomised control trials which included patients with upper gastrointestinal tract, head and neck and gynaecological malignancies found that there was 41 percent decline in the post-operative infectious complications and a reduction of about 2.38 days of hospital stay in patients who had received immune enhancing nutrition.

2. Waitzberg et al(82) analysed 17 randomised control trials(total of 2305 patients with 3 of those trials were blinded) on the effect of IMPACT (a commercially available immune enhancing formula containing omega-3 fatty acids, arginine and nucleotides) as compared to standard enteral diet given to patients undergoing

operation for upper gastrointestinal malignancy. They also compared the significance of giving immune enhancing nutrition either pre-operatively, peri-operatively or post-operatively. They compared the incidence of length of hospital stay, post-operative complications (infectious), mortality and cost of treatment among the groups. The use of commercial immune enhancing formula reduced the rate of post-operative infectious complications ($p < 0.0001$) , independent of the timing of administration of the immune enhancing formula (whether pre-operatively, peri-operatively or post-operatively). The length of hospital stay was significantly reduced (3.81 days lesser than the group receiving standard enteral nutrition) and this effect was not dependent on the timing of administration of the immune enhancing formula. It was also seen that there was a decrease in the incidence of post-operative wound infection, pneumonia, urinary tract infection and anastomotic leak. There was no difference in the mortality among the two groups.

3. Marik et al(83) analysed a total of 21 studies with 1918 patients which compared immunonutrition and standard enteral feeds in high-risk patients undergoing elective surgery. They found that patients receiving immunonutrition had significantly reduced infective complications, length of hospital stay and wound complications. There was no difference in mortality among the two groups. The effect of Immunonutrition was same whether it was administered pre-operatively, peri-operatively or post-operatively. It was also found that there was a synergistic action of arginine and omega-3 fatty acids when used together.

4. Mazaki et al(84) analysed 74 studies with a total of 7572 participants. He compared the effect of immune enhancing nutrition provided enterally, immune enhancing parenteral nutrition, standard enteral nutrition and standard parenteral nutrition on post-operative infectious complications in patients undergoing major gastrointestinal operations. They found that immune enhancing enteral nutrition was most efficacious in reducing post-operative infectious complications and was the best form of nutritional intervention. Standard parenteral nutrition group had the most inferior outcomes.

5. A Cochrane database review(85) of studies on the outcomes of pre-operative nutritional support in patients who were planned for upper GI surgeries in which a total of seven trials on enteral immune enhancing nutrition were included which showed a decrease in incidence of post-operative complications. But since there was identifiable bias among the studies the application of these results to all gastrointestinal surgery patients was limited. Moreover, they found some detrimental effects of Immunonutrition in patients who required critical care following surgery and hence they concluded that further studies may be required to determine which subset of patients undergoing gastrointestinal surgeries would be most benefitted with nutritional interventions.

6. Song et al(86) did a Bayesian network analysis of randomised control trials on the timing of administration of Immunonutrition (pre-operative, peri-operative or post-operative) compared with standard enteral nutrition in patients undergoing elective gastrointestinal surgeries. A total of 27 randomised control trials were analysed and it

was found that there was a decrease in post-operative infectious complications in the group receiving immunonutrition as compared to the group that received standard enteral nutrition. It showed that no statistically significant difference existed between pre-operative and peri-operative administration of immunonutrition. But one study with twenty nine patients showed that the rate of post-operative infectious complications was lower when Immunonutrition was administered perioperatively rather than post-operatively. On comparing the duration of hospital stay it was found that the group receiving immunonutrition had lesser mean duration of hospital stay than the group receiving standard enteral nutrition. On comparing the timing of administration of immune enhancing nutrition, there was no statistical difference between pre-operative and perioperative administration but there was a statistical difference between perioperative and post-operative administration of immunonutrition with a reduced mean duration of hospital stay in the perioperative immunonutrition group.

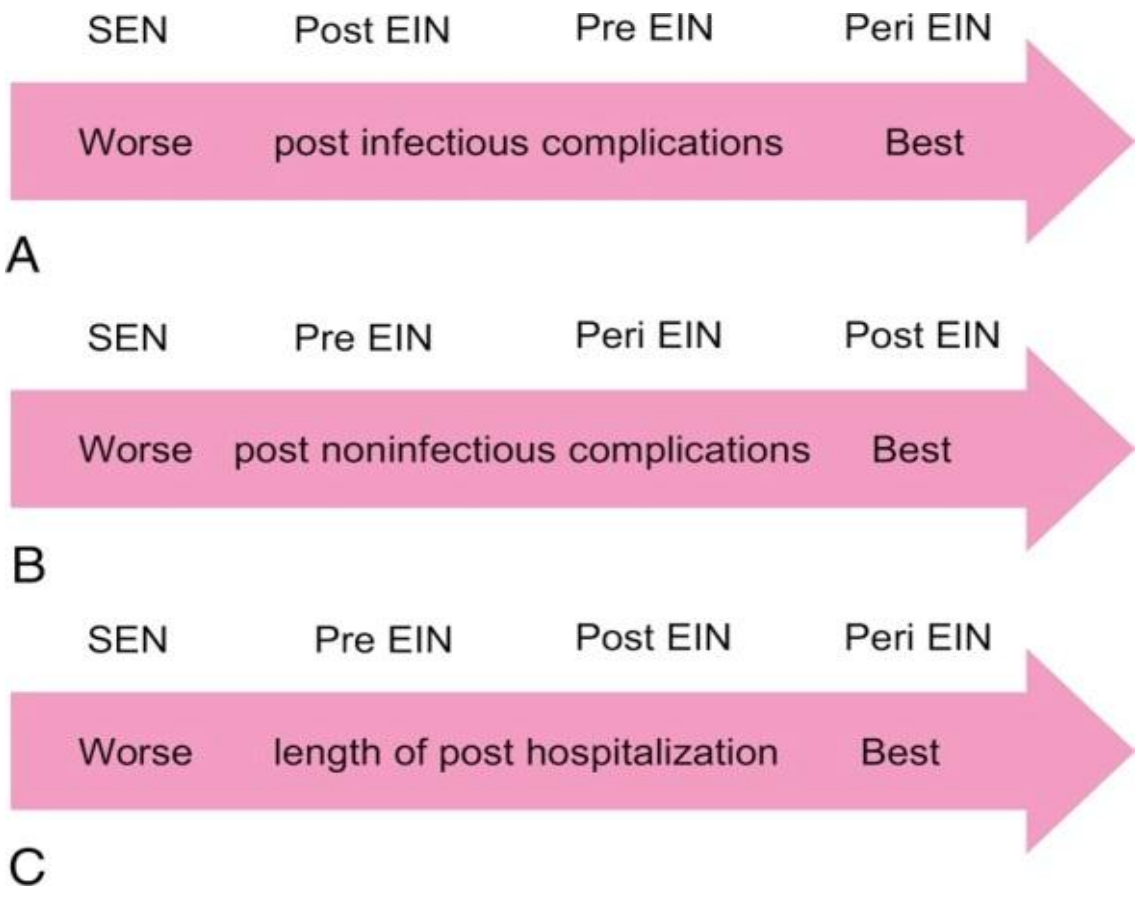


Image courtesy: Comparison of timing of administration of Immunonutrition(86)

(SEN – Standard enteral nutrition, EIN – Immune enhancing nutrition, Pre/Peri/Post-operatively)

Cost effectiveness of Immunonutrition

Despite improvement in surgical techniques, surgeries for cancer of esophagus are fraught with post-operative complications and significant morbidity. This leads to considerable economic burden on the patients as well as the healthcare system. There have been many studies on the cost effectiveness of Immunonutrition in patients planned for elective surgery. Senkal et al(87) in his study on Immunonutrition found that the complication rate in patients receiving immune enhancing nutrition was lower

than those receiving standard enteral nutrition, leading to cost-saving for the immunonutrition group (1503 Deutsche Marks vs 3587 Deutsche Marks). Strickland et al(88) made a national database evaluation(including about 1 million medical, surgical and trauma patients) of the cost-effectiveness of immune enhancing diet and found that use of immunonutrition reduced risk of infectious complications as well as hospital stay leading to savings of about $2066, $688 and $308 in medical, surgical and trauma patients respectively. In another study by Gianotti et al(89) it was found that the use of peri-operative Immunonutrition in patients with upper gastrointestinal tract cancers led to reduced post-operative complications with savings of approximately 2386 euros per complication-free patient. Many other studies have documented the cost effectiveness of Immunonutrition by reducing post-operative complication and mean days of hospital stay(82).

Current guidelines on Immunonutrition

As per American Society of Parenteral and Enteral Nutrition (ASPEN)(90) recommendations, patients who undergo head and neck, abdominal cancer surgery, trauma or burns can receive enteral immune enhancing formulas containing glutamine, arginine, nucleotides and omega- 3 fatty acids. They also recommend that these commercially available formulas should be used with caution in patients with severe sepsis. European Society of Parenteral and Enteral Nutrition (ESPEN)(91) recommends that Immunonutrition be used in malnourished patients having head and neck or abdominal cancer planned for elective surgery. Moreover they recommend that immune enhancing nutrition should be started prior to surgery and continued for

five to seven days post-operatively. In 2012, the North America Surgical Nutrition Summit(92) laid down consensus guidelines on Immunonutrition use in patients undergoing surgery. They recommended use of immune enhancing formulas five days prior to surgery (500-1000ml per day) and to continue the same for at least five days post-operatively.

From the above stated studies and meta-analyses it can be inferred that, Immunonutrition is helpful in reducing infectious post-operative complications and duration of hospital stay in patients undergoing elective gastrointestinal surgeries. Moreover, the benfit is more pronounced in malnourished subjects and when the immunonutrients are administered perioperatively. The role of Immunonutrition in patients with carcinoma esophagus undergoing elective esophagectomy is studied in only a few randomised control trials out of which some trials have showed indirect benefit in form of improved humoral immunity(65) while some other studies and meta-analyses have shown a reduction in post-esophagectomy complications (mostly infectious) but the results were not statistically significant(71). All the studies on patients undergoing esophagectomy had used either arginine or omega-3 fatty acid containing commercial formulas. In this study, an endeavour is made to use another immunonutrient namely, Glutamine and its effect on esophageal cancer patients undergoing esophagectomy.

Glutamine as an immunonutrient

L-Glutamine is the most abundant amino acid in intracellular and extracellular compartments of the body. It is however lost from the body and muscle stores in

conditions of severe metabolic stress like sepsis or major surgery. In these conditions, it is required to make up for the deficiency created as a result of high demand. Therefore, in these situations that it becomes a conditionally essential amino acid(93). Glutamine acts as energy providing substrate for rapidly dividing cells like intestinal mucosal and lymphocytes(94). Glutamine is a precursor of glutathione along with glycine and cysteine. Glutathione is an important anti-oxidant in the body and hence glutamine supplementation may help in protecting against oxidative stress and damage. Glutamine induces increased expression of heat shock proteins in the body which protect tissues against injury and cellular apoptosis in conditions of metabolic stress like trauma or major surgery. Thus supplementation of glutamine may be beneficial in these patients. Ziegler et al(95) studied the effect of parenteral glutamine supplementation in patients admitted to an ICU and found a higher concentration of heat shock proteins in those supplemented with glutamine. This correlated with decrease in ICU stay. Glutamine has also been found to reduce insulin resistance and is a precursor of arginine in the body by nitrogen transfer via citrulline. Glutamine downregulates the expression of toll-like receptors which get induced in the intestinal cells following exposure to lipopolysaccharide present in gram negative bacteria(96). Toll-like receptors are known to induce cytokines like TNF-α, IL-1, IL-6 and cause injury to the intestinal mucosa. Hence, supplementation of glutamine may protect against intestinal mucosal injury that can be caused as a result of gram negative septicaemia. Normal plasma range of glutamine is 500-750 µmol/L. The plasma levels of glutamine can fall below 500µmol/l during periods of heavy exercise training leading to overtraining syndrome as the deficit takes a long time to be replenished

without external supplementation of glutamine(97). In catabolic conditions like sepsis, major surgery or trauma, there may be a fall of intracellular and plasma glutamine levels to 50 percent and 30 percent of its normal values and this far exceeds the capability of body to synthesize glutamine. Hence glutamine replacement is of utmost importance in these conditions(98). Glutamine is also required for growth and multiplication of cell lines in culture. The most important effect of glutamine is on the gastrointestinal tract. The mucosa of the gastrointestinal tract is most important site of glutamine metabolism. It is an important energy providing nutrient in the intestine accounting for about 35 percent of the total metabolic needs. Glutamine also modulates many other protective function in the gastrointestinal tract and plays a major role in maintaining integrity of gut mucosa(99). The gastrointestinal tract plays an important role in catabolic response seen during stress and injury. In periods of stress like major surgery or trauma, deficiency of glutamine can lead to mucosal atrophy. Oral glutamine supplements lead to increase in villous height and prevent mucosal atrophy in patients receiving prolonged parenteral nutrition(100). Glutamine has also been seen to increase the absorption of water, electrolytes and nutrients in animals with experimentally induced diarrhoea. It also protects the intestinal mucosa from the harmful effects of ammonia which is produced as a result of nutrient breakdown in the mucosal cells. Glutamine prevents against the harmful effects of radiation and chemotherapy in patient with malignancy. Radiation and chemotherapy cause a decrease in lymphocyte counts as well as mucosal injury. Glutamine protects against mucosal injury caused by radiation, chemotherapy, sepsis or surgical stress by increasing mucosal protein synthesis and a reduction in proteolysis(101). The

gastrointestinal mucosa acts as a mechanical and immunogenic barrier to numerous harmful organisms as well as toxins in the diet. This barrier function is found to be compromised in conditions of direct mucosal injury or in conditions of increased stress like major surgery, burns or trauma leading to increase permeability to toxins, pathogens and bacterial endotoxins. This results in increased inflammation, sepsis and eventually ends with multiorgan dysfunction syndrome(102). There have been a large number of studies which have shown glutamine supplementation to be beneficial in improving the barrier function of intestinal mucosa after severe stress. It reduces the increase in gut permeability and systemic inflammation caused by major surgery(103). Numerous studies have shown the effect of glutamine in maintenance of epithelial tight junctions in the gut mucosa during periods of stress. This has also been validated in experimental studies on Caco-2 cell monolayers and on human colonic mucosa treated with acetaldehyde where glutamine has been shown to maintain integrity of the epithelial tight junctions(104). Glutamine has been shown to increase neutrophil phagocytosis and intermediate production of reactive oxygen in vitro in patients who had undergone major surgery(105). Thus from the above discussion it is evident that glutamine plays an important role in immunomodulation and gut protective function and hence has an important role as an immunonutrient.

Dose and mode of supplementation of Glutamine

Glutamine has a low stability in aqueous environment and hence is usually coupled with other amino acids like alanine or glycine as a dipeptide to decrease its degradability. It has also been seen that there is better concentration of arterial glutamine when alanine-glutamine is parenterally administered instead of just free glutamine(96). Glutamine is easily degraded into toxic pyroglutamate in solution during heat sterilisation and hence glutamine preparations are packed dry and reconstituted just before administration. Oral glutamine administered at a dose of 0.3gm/kg per day has shown to preserve intestinal mucosal integrity and decrease the incidence of sepsis and necrotising enterocolitis in pre-term infants. Houdjik et al(106) showed that enterally supplemented glutamine at a dose of 30.5gms per 100gms of protein intake reduced the incidence of pneumonia, bacteraemia and sepsis in patients with multiple trauma. Cetinbas et al(107) showed that administration of total parenteral nutrition which was enriched with glutamine, in patients with systemic inflammatory response syndrome at a dose of 0.4gm/kg/day decreased neutrophil and natural killer cell count and increased lymphocyte counts (though not statistically significant, it may lead to improvement of immune system). Most of the studies have used commercially available formula containing both arginine and glutamine and have shown improved clinical outcomes in malnourished patients with upper gastrointestinal cancer undergoing surgery. Some of the studies that have used glutamine as a single immunonutrient are as follows:

1. Lorenz et al(108) studied the effect of early enteral supplementation of glutamine in patients with multiple trauma and extensive surgery (major head and neck surgeries). They found that the group of patients who received early enteral glutamine supplements had increased lymphocyte counts, faster normalisation of pro-inflammatory marker levels in the blood, reduced infectious complications and reduced ICU stay.

2. Garcia-de-Lorenzo et al(109) in a systemic review of studies on glutamine as a single immunomodulating agent found that glutamine enriched diet was well tolerated, showed improvement of outcomes in critical care and polytrauma patients. They recommended glutamine supplementation at the rate of 20-30gms/day for at least five days (Grade C recommendation).

Studies have shown that glutamine is more potent than arginine supplementation in malnourished patients. Morais and colleagues(110) compared the effect of glutamine and arginine on esophageal cancer patients, undergoing elective surgery and found that patients who received supplemental glutamine had reduced post-operative morbidity as well as lesser number of days of hospital stay. The patients who had received arginine however, had a greater increase in serum albumin as compared to patients who received glutamine. There were no harmful side-effects attributed to the therapy. In another study by Marton et al(111) a comparison was made between glutamine supplementation and standard nutrition on the post-operative mortality, morbidity and systemic inflammatory response syndrome on patients undergoing

esophagectomy. The two groups did not differ statistically in terms of the above stated factors.

Glutamine is an useful immunonutrient with many important physiological functions and that its importance increases in periods of catabolic stress like trauma and major surgery and there are numerous beneficial effects of its supplementation in patients who are undergoing major surgery. Though some studies have shown it to be of importance in esophageal cancer patients, undergoing esophagectomy, others have shown it to be of no use. Equivocally no studies have shown it to have harmful effects on patients undergoing major surgery or patients with trauma. There is a necessity for larger trials to prove the efficacy of this immunonutrient and this study is a small step towards that same direction.

MATERIALS AND METHODS

STUDY DESIGN: Prospective interventional study with retrospective control group approved by the Institutional Review Board (IRB) of Christian Medical College and Hospital, Vellore, Tamil Nadu. IRB study number – 9147F dated 12.11.2014 and fund no. 22Y570. The CTRI Regd. No. is REF/2016/09/012194.

SETTING: The setting of the study was Department of Surgery Unit III (Department of Upper GI and Bariatric Surgery), Christian Medical College, Vellore, Tamil Nadu. Christian Medical College, Vellore is a tertiary care hospital established in 1900. It is 2700 bedded hospital with multiple specialities and superspecialities. The department of Upper GI and Bariatric surgery caters to a large number of esophageal and gastric cancer patients from all over India. About 20 to 25 esophagectomies are done each year in this department. Hence, this department was an appropriate setting for doing this study.

METHODOLOGY :

1. SAMPLE SIZE: The total sample size was calculated as 44 out which 22 patients were prospectively studied and 22 patients were retrospective controls. However, only 21 prospective patients could be recruited into the study. A few patients were recruited into the study but were deemed inoperable and hence were excluded from the study. However, study will be ongoing till a total of 22 prospective cases are done. The sample size calculation was based on a study done by Senkal et al on the Outcome and Cost-effectiveness of Peri-operative Enteral Immunonutrition on patients undergoing

elective Upper GI surgery. The alpha level for the study was 5% and power of study was 80%.

2. INCLUSION CRITERIA FOR THE STUDY:

Patients diagnosed to have esophageal carcinoma, undergoing elective esophagectomy in Surgery Unit 3.

3. EXCLUSION CRITERIA FOR THE STUDY:

1. Patients not consenting for the study.
2. Patients with known allergies or intolerance to the immunonutrient.
3. Patients with non-resectable esophageal cancer.

4. SAMPLING AND CONSENT:

All patients with esophageal carcinoma who were fit to undergo an esophagectomy and were admitted under Surgery unit III were included in the study.

An informed consent was taken from the patient prior to starting on glutamine powder as per the Institutional Review Board guidelines. The glutamine powder used in this study was Kabimmune sachet manufactured by Fresenius Kabi. Each sachet with 15 grams of powder contained 10 grams of L- Glutamine. The total number of days of hospital stay and other relevant clinical information were taken from the clinical workstation.

The consent form and the patient information sheets are attached (APPENDIX 1).

5. TIMING:

The study period was from January 2015 to August 2016. The patients who were diagnosed cases of esophageal cancer and were operable after neoadjuvant chemoradiotherapy were recruited for the study. They were started on Glutamine powder at a dose of 0.3gms/kg/day four days prior to surgery and this was continued post-operatively for fourteen days. Consenting was done by the principle investigator. Pre-operatively, patients were instructed about the method of glutamine powder intake. Post-operatively, they were started on the powder through a feeding jejunostomy tube which was placed at the time of surgery and subsequently, the powder was given orally.

6. VARIABLES:

The various variables studied were the patient's age, gender, body mass index, ASA score, hemoglobin levels, total leucocyte counts, percentage of neutrophils and lymphocytes.

The primary outcome of this study was to observe whether peri-operative administration of immune enhancing nutrition was associated with a reduction in total length of hospital stay.

The secondary outcome was to observe the effect of peri-operative immune enhancing nutrition on post-operative complications mainly pneumonia, wound infection and anastomotic leak.

7. STANDARD OPERATING PROCEDURE:

- Patients diagnosed to have operable esophageal carcinoma and planned for elective esophagectomy under Surgery Unit III were recruited into the study, pre-operatively, after taking an informed consent.
- The patients were assessed for nutritional status pre-operatively by measuring body mass index, hemoglobin levels and serum albumin. The immunological status was assessed by the total leucocyte count and the percentage of neutrophils and lymphocytes on differential count.
- They were started on Glutamine powder at a dose of 0.3 g/kg/day (approximately two sachets per day) four days prior to surgery. The powder was taken as a solution in 200ml of water. For people who were unable to take orally, this was given by indwelling nasogastric tubes (placed prior to starting neoadjuvant chemoradiotherapy).
- Post-operatively, they were started on Glutamine at a same dose. This was given by a feeding jejunostomy tube which was placed intra-operatively for feeding purposes. This was changed to oral route once the patient was able to tolerate oral feeds. This was continued for a total of two week post-operatively.
- Data was collected in regards to the total length of hospital stay, days of stay in an intensive care unit and post-operative complications (post-operative pneumonia/atelectasis, wound infection and anastomotic leak).
- The data so obtained was compared with the data from the control group which comprised of patients with esophageal carcinoma who had undergone esophagectomy under Surgery unit III from January, 2013 to December, 2014.

These patients had not received immunonutrition. The data was compared statistically to determine the effect of peri-operative immunomodulation using Glutamine.

8. PERSONNEL:

a) Person taking consent and instructing about the administration of the drug was the PG resident doing the thesis

b) Healthcare personnel in the ward (mainly nurses) were involved in post-operative administration of Glutamine powder via feeding jejunostomy tube. They also trained the patient's relatives in preparation and administration of glutamine sachet, through the feeding jejunostomy tube.

9. IMMUNONUTRIENT USED:

L-Glutamine sachet manufactured by Fresenius Kabi India Ltd and sold under the brand name Kabimmune™.

RESULTS: The summary of results is as follows:

OUTCOMES	IMMUNONUTRITION		P VALUE
	YES(n=21)	NO(n=22)	
HOSPITAL STAY MEDIAN(IQR)	12 (11-16)	16 (13-22)	0.004
ICU STAY MEDIAN(IQR)	2 (2-3)	2 (2-2)	0.295
PNEUMONIA n (%)	2 (9.5)	7 (31.8)	0.132
WOUND INFECTION n (%)	1 (4.8)	1 (4.5)	>0.999
ANASTOMOTIC LEAK n (%)	1 (4.8)	4 (18.2)	0.345

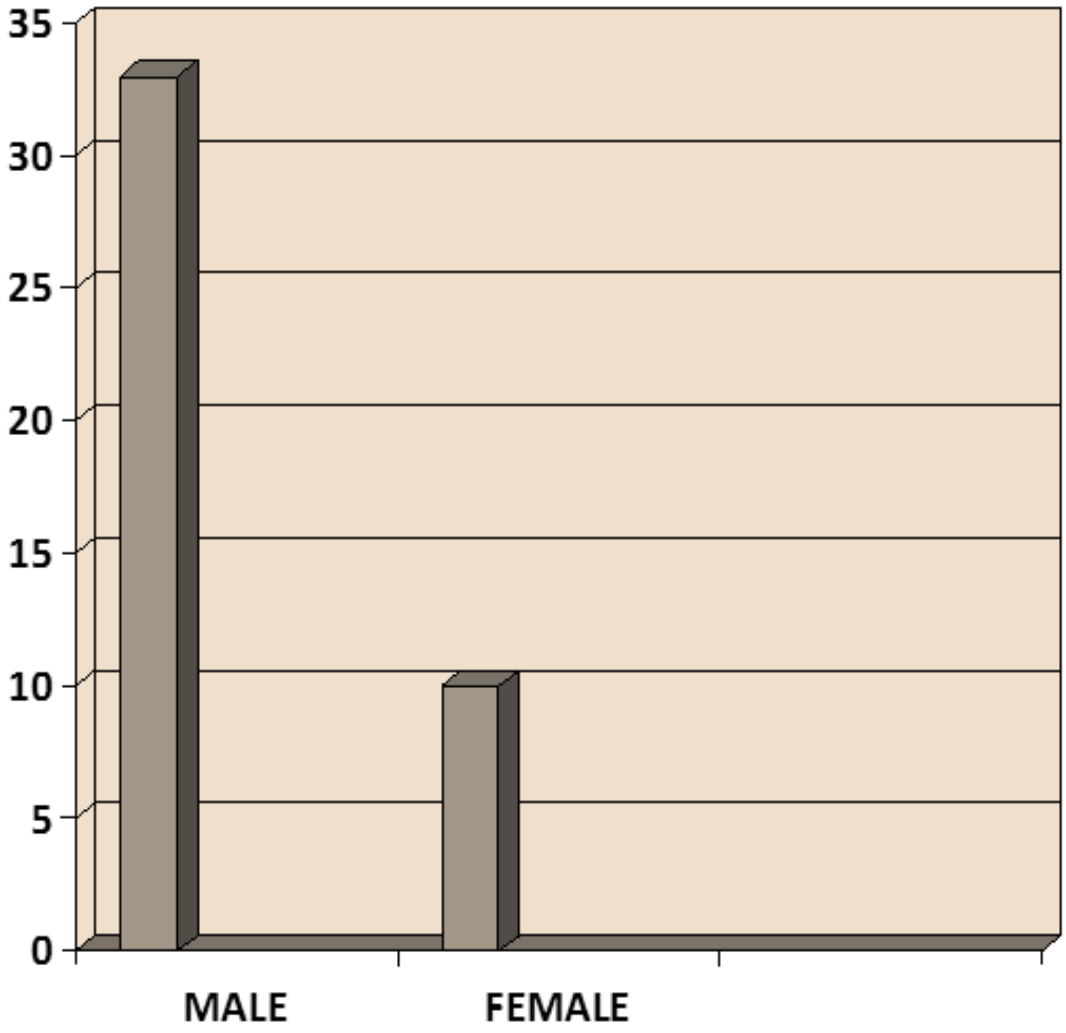
Overall Frequency Table:

Immunonutrition		Age	BMI	TLC	HB	N %	L %	SA
Yes	Valid	21	21	21	21	21	21	21
	Missing	0	0	0	0	0	0	0
Mean		55.95	21.9481	8166.67	11.43	62.67	23.67	3.843
Std. Deviation		8.453	3.79955	3294.592	1.326	12.737	11.240	.5861
Minimum		37	14.20	4300	9	34	7	2.5
Maximum		67	30.70	16800	14	90	46	4.5
Percentiles	25	48.50	18.8000	6200.00	10.50	54.50	13.50	3.450
	50	57.00	22.0000	7000.00	11.00	62.00	21.00	4.000
	75	62.50	24.9500	9350.00	12.00	71.00	30.00	4.400
No	Valid	22	22	22	22	22	22	22
	Missing	0	0	0	0	0	0	0
Mean		53.32	21.1636	6959.09	12.36	58.09	23.50	3.977
Std. Deviation		9.594	3.83574	2602.500	1.293	11.641	9.556	.4545
Minimum		33	16.30	3100	9	32	5	2.5
Maximum		66	32.70	13700	14	79	42	4.6
Percentiles	25	48.25	17.9250	5425.00	11.00	48.00	14.00	3.775
	50	54.50	20.5000	6850.00	13.00	60.00	23.00	3.950
	75	63.00	23.4500	8150.00	13.00	65.25	30.25	4.400

Total Number of Esophageal Carcinoma Patients: 43

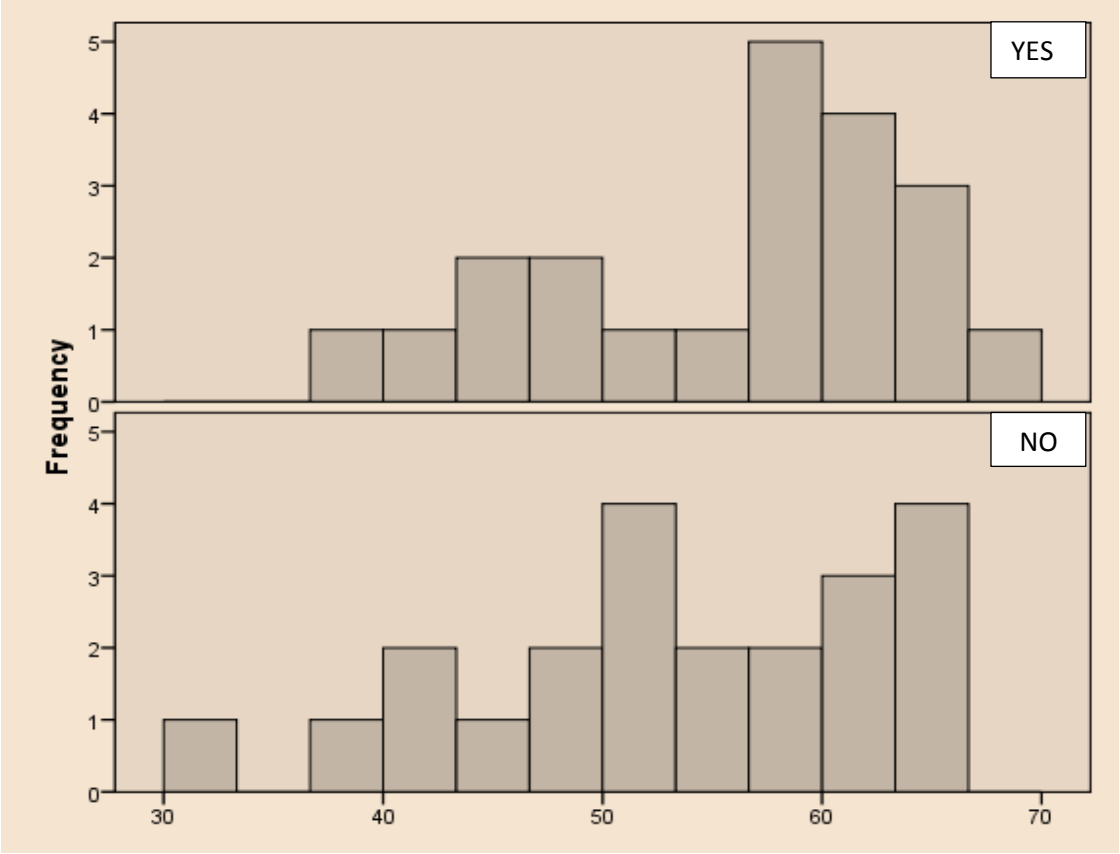
A) Gender:

Males – 33 and Females – 10



B) Age of Patients:

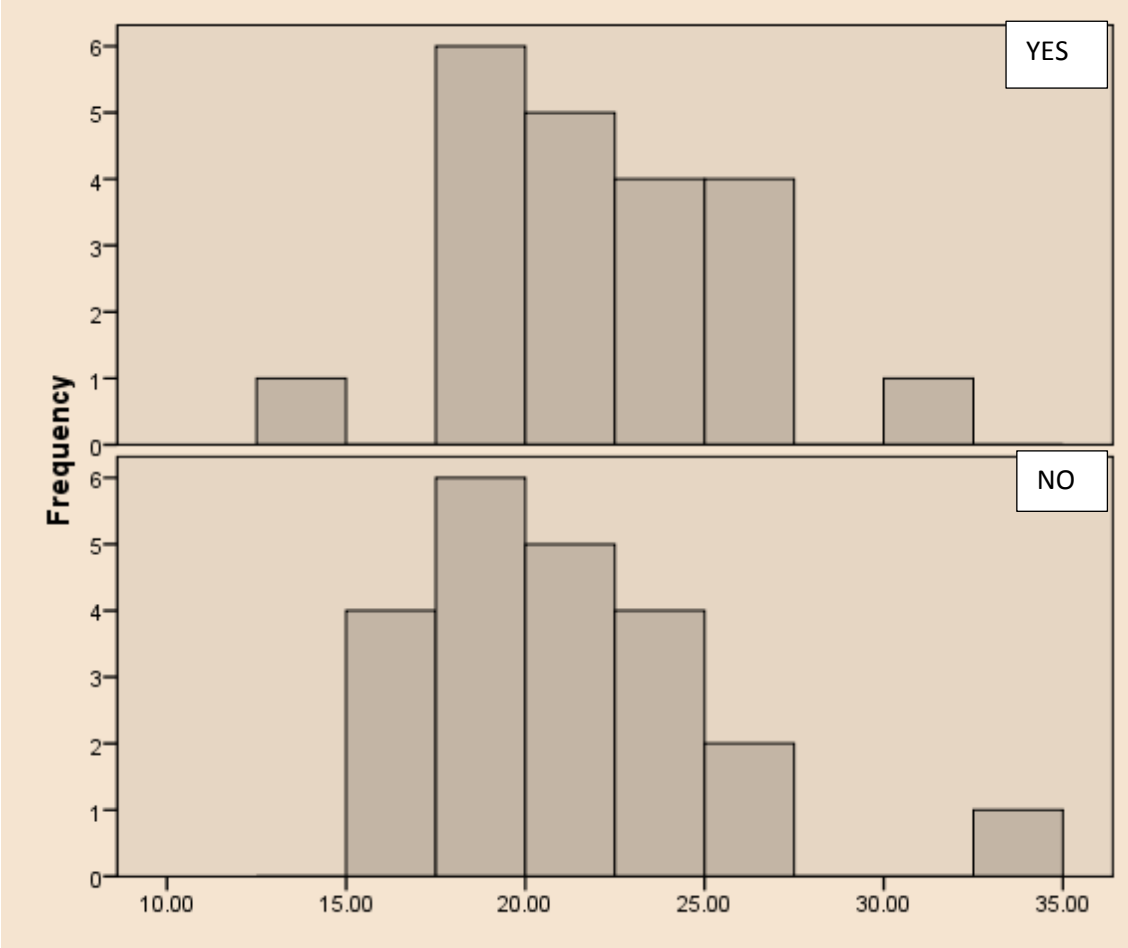
The mean age of patients in the immunonutrition group was 55.95 (minimum 37 and maximun 67) and in the control group it was 53.52 (minimum 33 and maximum 66)



AGE OF PATIENTS

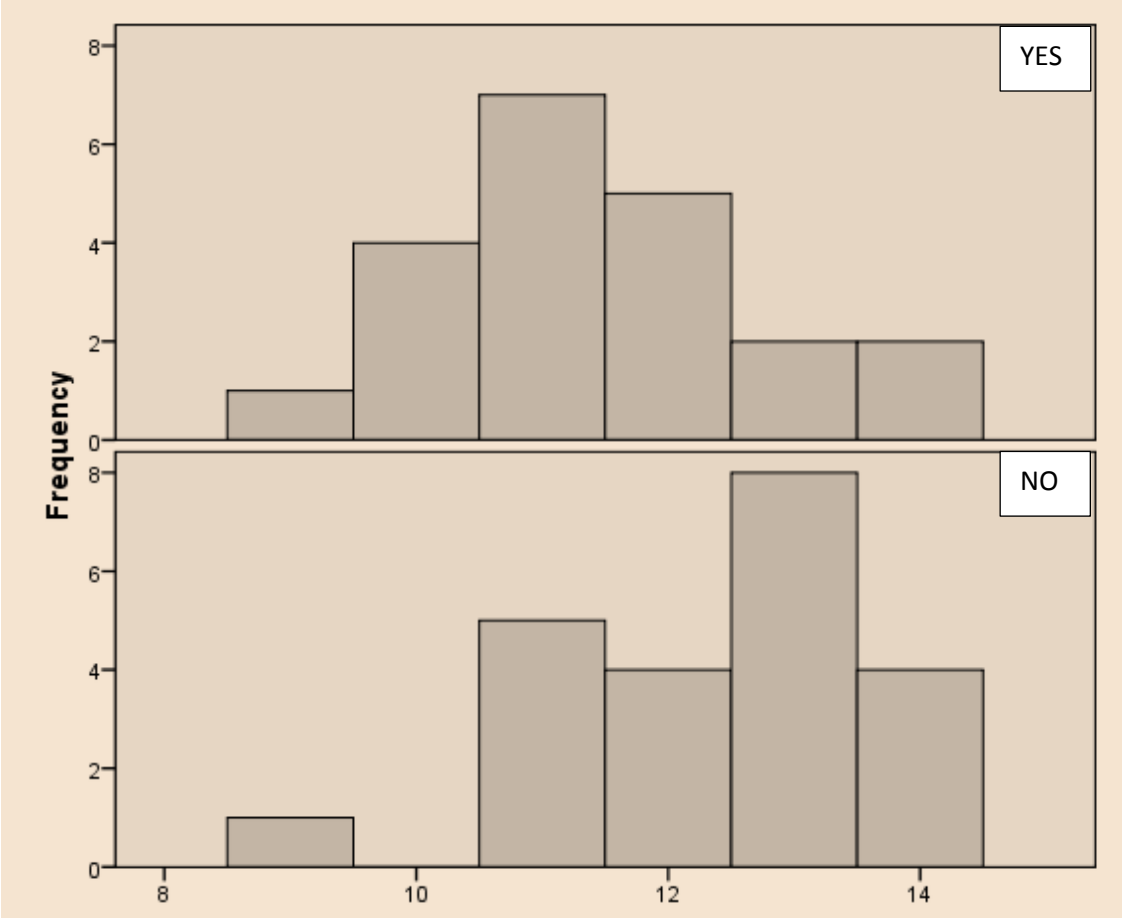
C) Body Mass Index (BMI):

The mean BMI of patients in the immunonutrition group was 21.95 (minimum 14.20 and maximum 30.70) and in the control group it was 21.16 (minimum 16.3 and maximum 32.70).



D) Haemoglobin Levels:

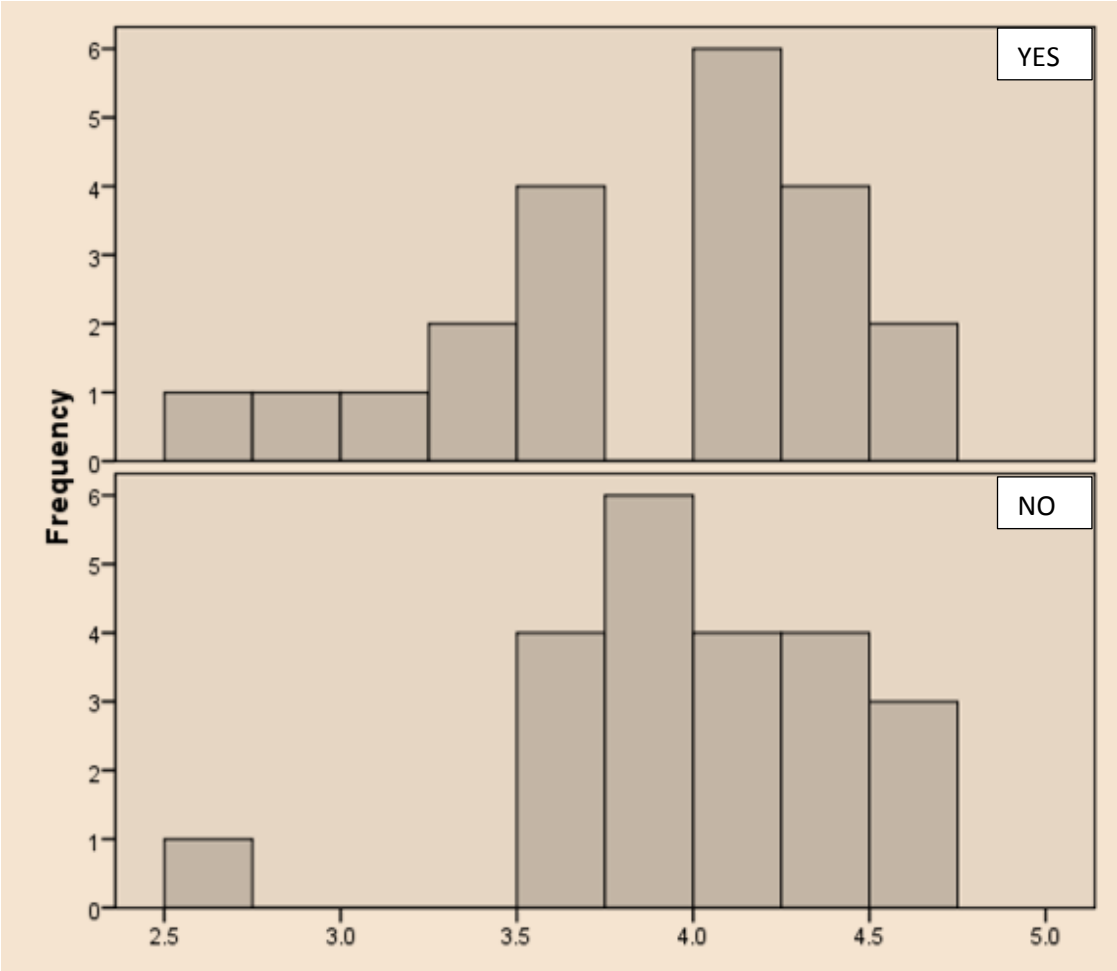
The mean haemoglobin levels in the group taking immunonutrition was 11.43 (minimum 9gm% and maximum 14gm%) and in the control group it was 12.36 (minimum 9gm% and maximum 14gm%)



HAEMOGLOBIN LEVELS

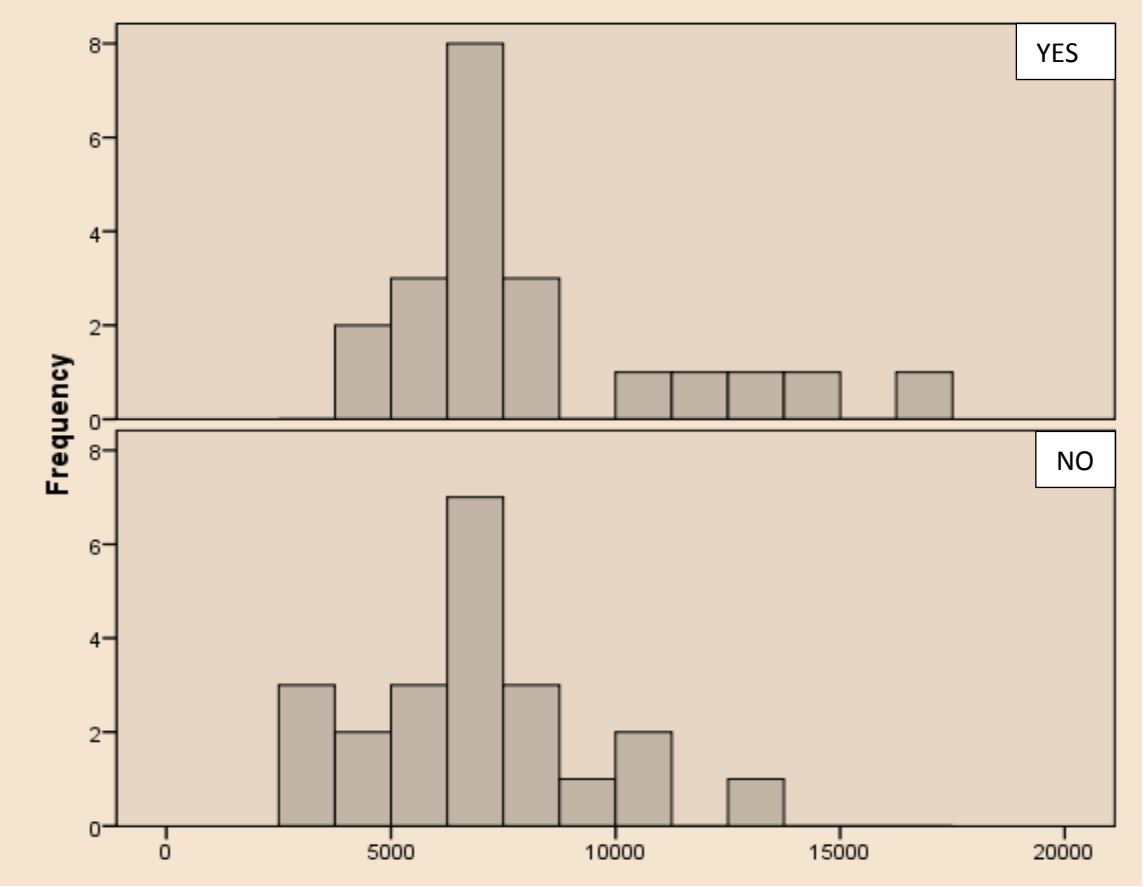
E) Serum Albumin levels:

The mean serum albumin levels in the immunonutrition group was 3.84g/dl (minimum 2.5g/dl and maximum 4.5g/dl) and in the control group, the mean serum albumin level was 3.97g/dl (minimum 2.5g/dl and maximum 4.6g/dl).



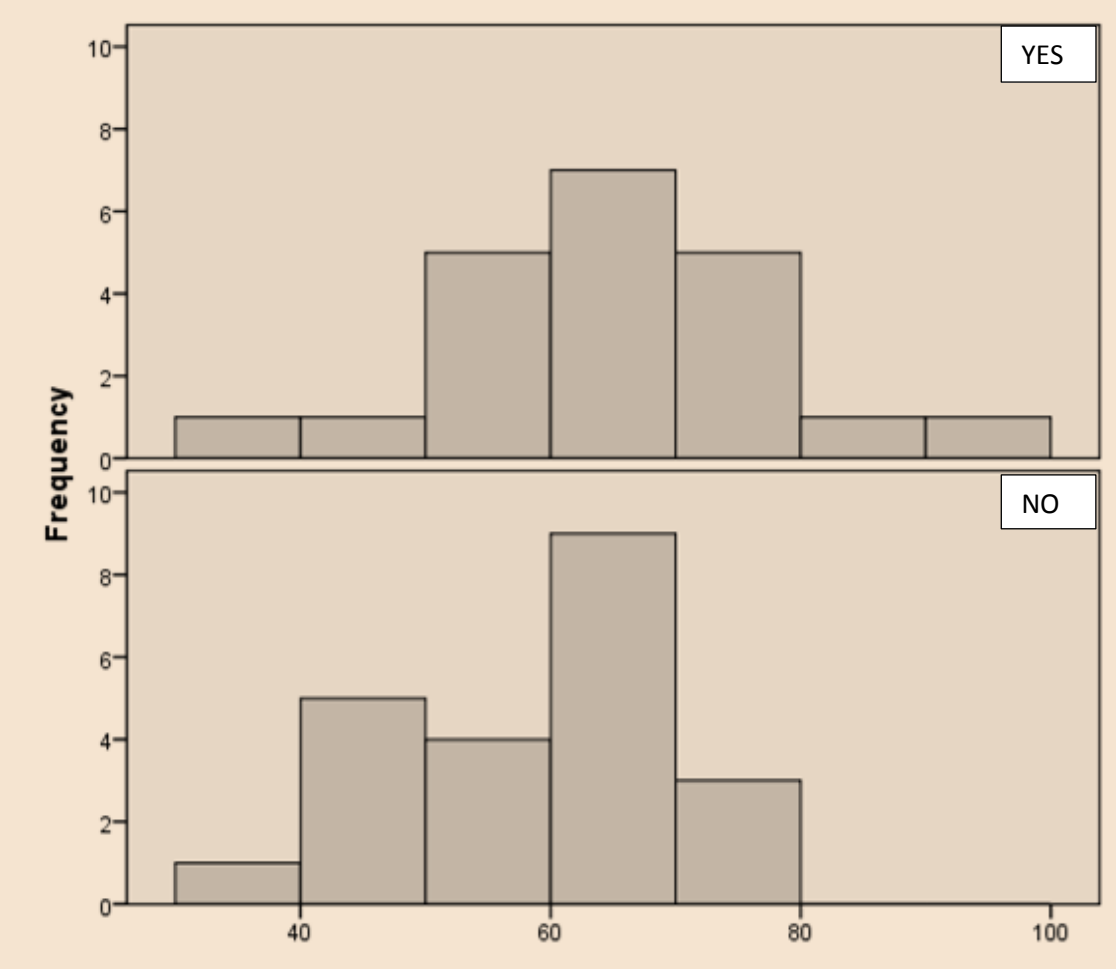
F) Total Leucocyte Count:

The mean total leucocyte count in the Immunonutrition group was 8166.67 (minimum – 4300 and maximum – 16800) and in the control group it was 6959.09 (minimum – 3100 and maximum – 13700).



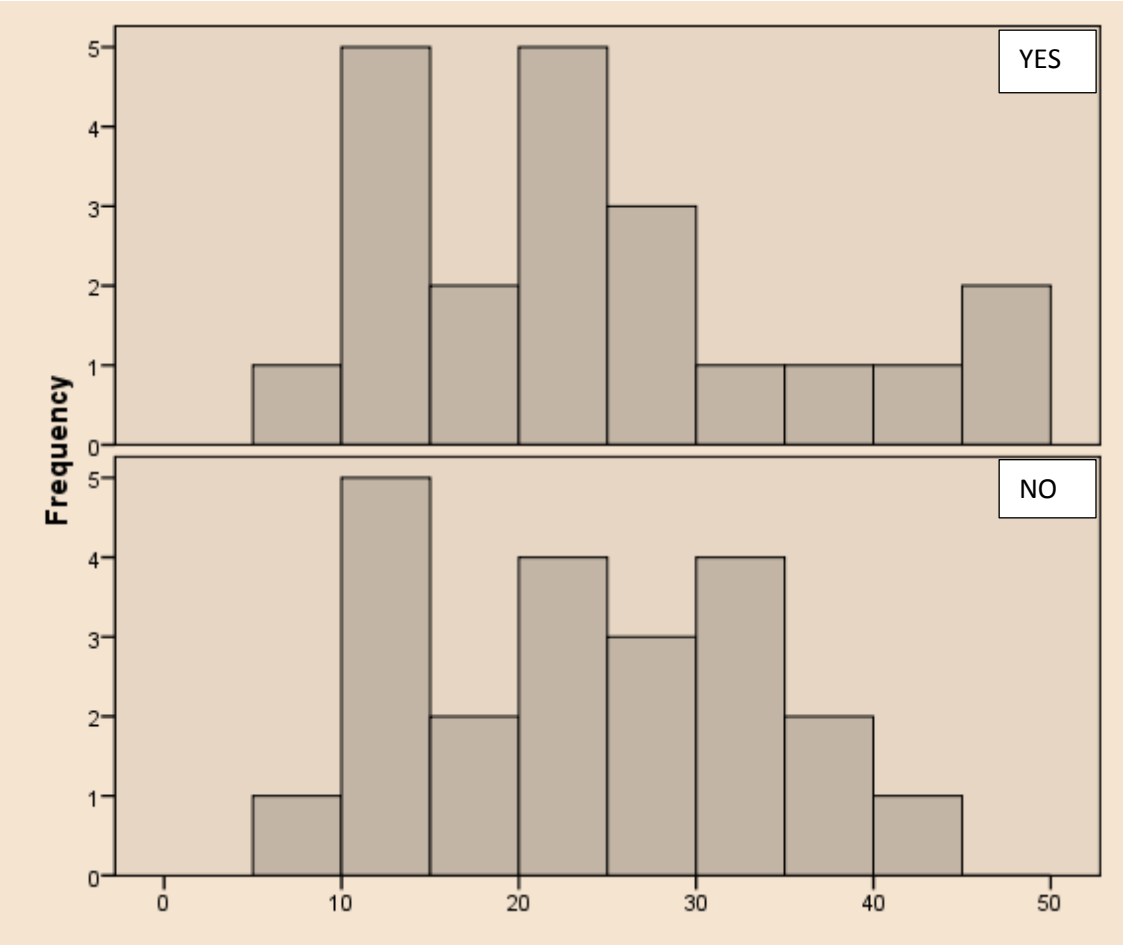
G) Percentage of neutrophils:

The mean percentage of neutrophils in the Immunonutrition group was 62.67 (minimum 34 percent and maximum 90 percent) while in the control group it was 58.09 (minimum 32 percent and maximum 79 percent).



F) Percentage of lymphocytes:

The percentage of lymphocytes in the Immunonutrition group was 23.67 (minimum 7 percent and maximum 46 percent) and in the control group it was 23.50 (minimum 5 percent and maximum 42 percent).



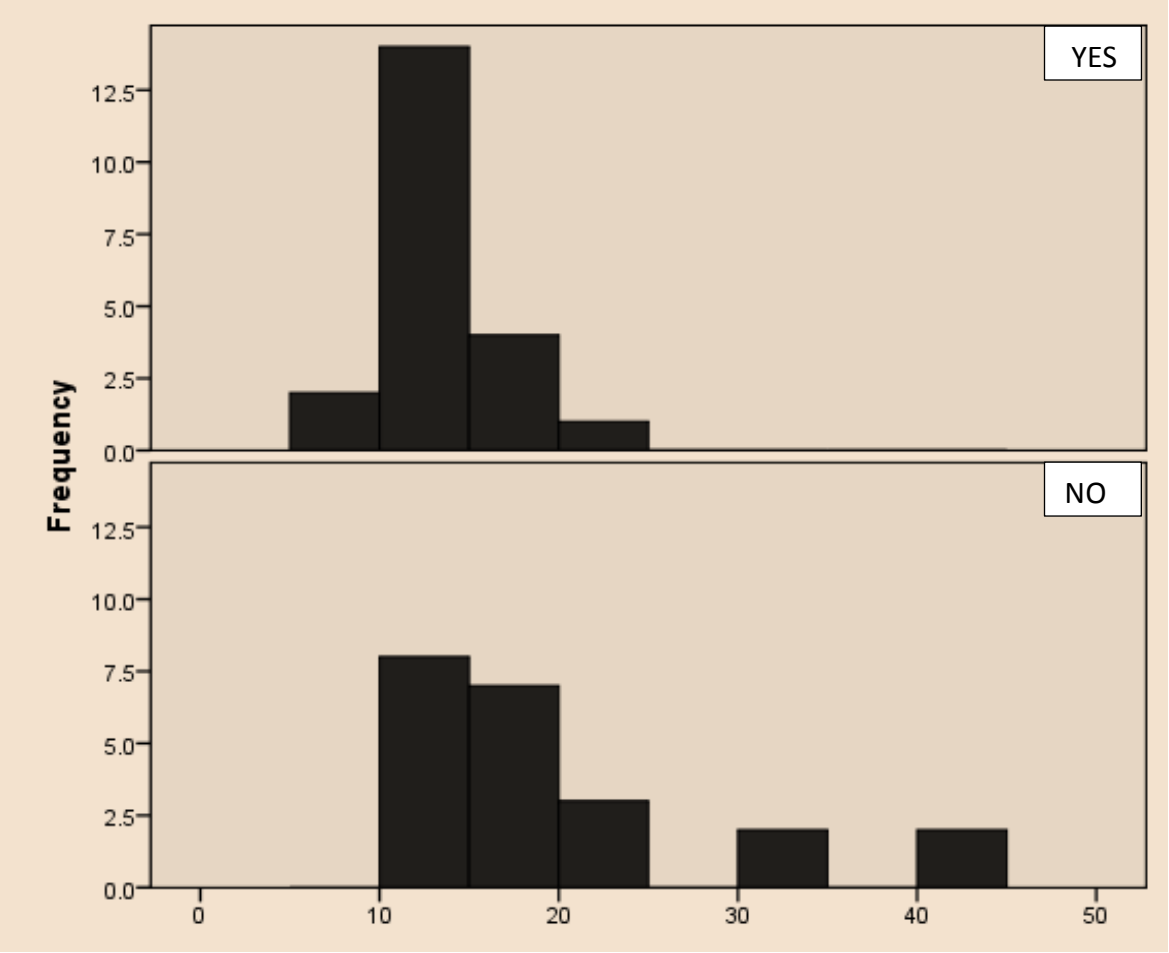
G) Total Duration Of Hospital Stay:

The mean total length of hospital stay in the immunonutrition group was 13.19 days and in the control group it was 19.36 days.

Frequency Table:

Yes	(N)	Valid	21
		Missing	0
	Mean		13.19
	Std. Deviation		3.683
	Minimum		8
	Maximum		21
	Percentiles	25	10.50
		50	12.00
		75	15.50
No	(N)	Valid	22
		Missing	0
	Mean		19.36
	Std. Deviation		9.394
	Minimum		11
	Maximum		44
	Percentiles	25	13.00
		50	**15.50**
		75	22.00

Graph:


YES
NO
Frequency
12.5
10.0
7.5
5.0
2.5
0.0
0
10
20
30
40
50
TOTAL LENGTH OF HOSPITAL STAY

I) Post-operative Pneumonia:

Crosstab

			Post-operative Pneumonia		
			Yes	No	Total
Immunonutrition	Yes	Count	2	19	21
		% within Immunonutrition	9.5%	90.5%	100.0%
	No	Count	7	15	22
		% within Immunonutrition	31.8%	68.2%	100.0%
Total		Count	9	34	43
		% within Immunonutrition	20.9%	79.1%	100.0%

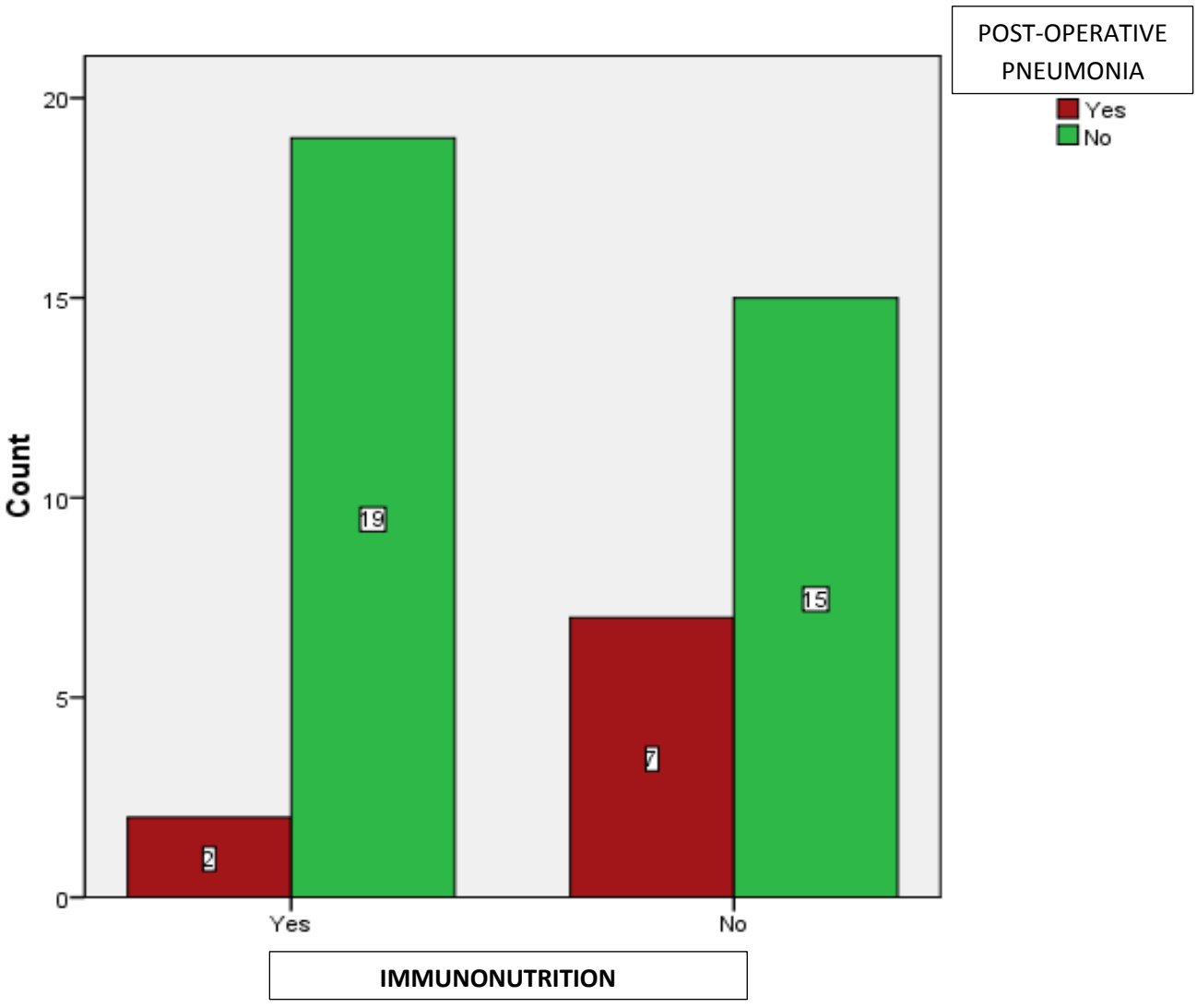
Chi-Square Tests

	Value	Df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	3.227[a]	1	.072		
Continuity Correction[b]	2.020	1	.155		
Likelihood Ratio	3.390	1	.066		
Fisher's Exact Test				.132	.076
Linear-by-Linear Association	3.152	1	.076		
N of Valid Cases[b]	43				

a. 2 cells (50.0%) have expected count less than 5. The minimum expected count is 4.40.

b. Computed only for a 2x2 table

Graph:


POST-OPERATIVE PNEUMONIA
Yes
No
Count
20
15
10
5
0
19
2
15
7
Yes
No
IMMUNONUTRITION

G) Post-operative Wound Infection:

Crosstab

			Post-op wound infection		
			Yes	no	Total
Immunonutrition	Yes	Count	1	20	21
		% within Immunonutrition	4.8%	95.2%	100.0%
	No	Count	1	21	22
		% within Immunonutrition	4.5%	95.5%	100.0%
Total		Count	2	41	43
		% within Immunonutrition	4.7%	95.3%	100.0%

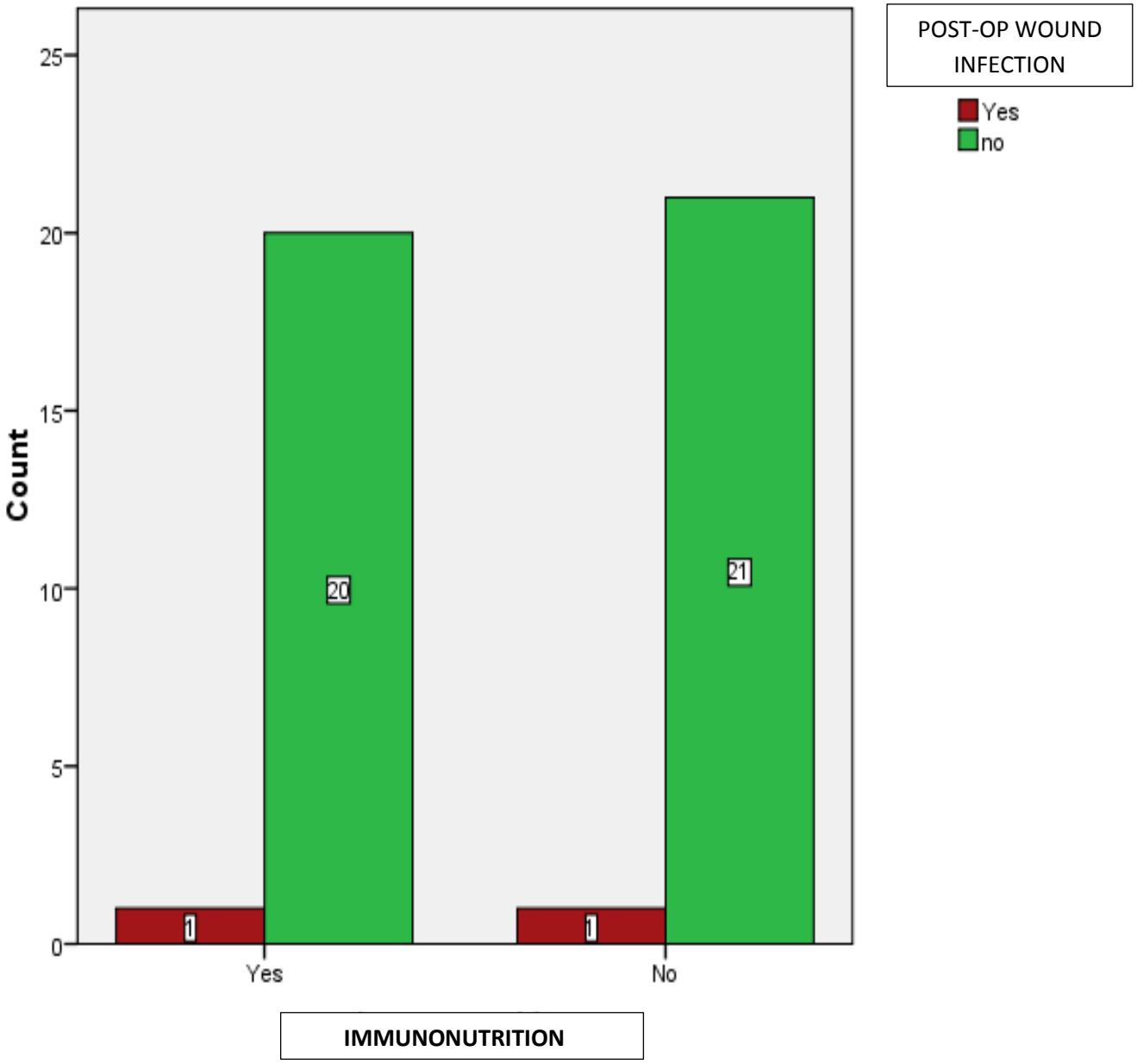
Chi-Square Tests

	Value	Df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.001[a]	1	.973		
Continuity Correction[b]	.000	1	1.000		
Likelihood Ratio	.001	1	.973		
Fisher's Exact Test				1.000	.744
Linear-by-Linear Association	.001	1	.973		
No. of Valid Cases[b]	43				

a. 2 cells (50.0%) have expected count less than 5. The minimum expected count is .98.

b. Computed only for a 2x2 table

Graph:


POST-OP WOUND INFECTION
Yes
no
Count
25
20
15
10
5
0
1
20
1
21
Yes
No
IMMUNONUTRITION

H) Anastomotic Leak:

Crosstab

			Anastomotic leak		
			Yes	No	Total
Immunonutrition	Yes	Count	1	20	21
		% within Immunonutrition	4.8%	95.2%	100.0%
	No	Count	4	18	22
		% within Immunonutrition	18.2%	81.8%	100.0%
Total		Count	5	38	43
		% within Immunonutrition	11.6%	88.4%	100.0%

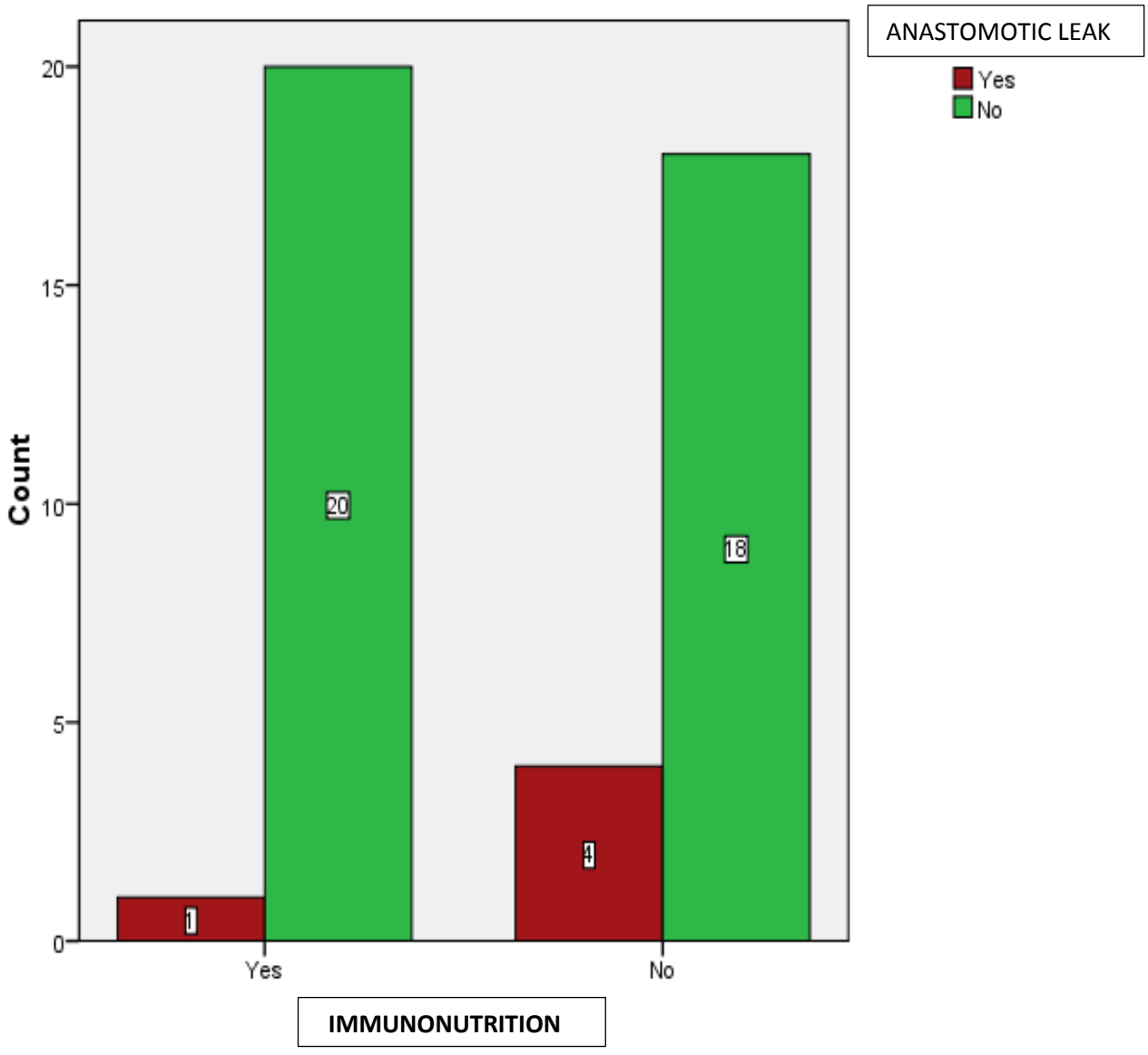
Chi-Square Tests

	Value	Df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	1.883[a]	1	.170		
Continuity Correction[b]	.803	1	.370		
Likelihood Ratio	2.010	1	.156		
Fisher's Exact Test				.345	.187
Linear-by-Linear Association	1.839	1	.175		
N of Valid Cases[b]	43				

a. 2 cells (50.0%) have expected count less than 5. The minimum expected count is 2.44.

b. Computed only for a 2x2 table

Graph:


ANASTOMOTIC LEAK
Yes
No
Count
20
15
10
5
0
20
18
4
1
Yes
No
IMMUNONUTRITION

DISCUSSION

A total of 43 patients were studied (21 cases and 22 controls). There were 33 male and 10 female patients. The mean age of the cases was 55.95 +/- 8.45 years and that of the controls was 53.32 +/- 9.59 years. From the data collected it was seen that the cases as well as the controls were similar with repect to age. The mean body mass index, hemoglobin levels and serum albumin levels were also comparable (BMI – 21.95 v/s 21.16, Hb – 11.43 v/s 12.36, Albumin – 3.84 v/s 3.97). The cases were given Glutamine powder at a dose of 0.3mg/kg/day,dissolved in water. This was started four days prior to surgery and was restarted post-operatively through a feeding jejunostomy tube, placed intra-operatively. There were no harmful effects of the administered immunonutrient. The two groups were compared in terms of total duration of hospital stay and incidence of post-operative complications.

A statistically significant reduction in the total duration of hospital stay in the intervention group was noted as compared to the control (13.19 +/- 3.68 days in the immunonutrition group as compared with 19.38 +/- 9.394, p= 0.004) . Although the total duration of ICU stay was similar in both groups (2.29 +/- 0.784 days in the immunonutrition group as compared with 2.23+/-1.115 days) there was a decrease in the incidence of post-operative pneumonia as well as anastomotic leak in the group receiving immunonutrition. However this was not statistically significant. The incidence of wound infection was also similar in both groups.

From this study it seems that immunonutrition helps in reducing the total duration of hospital stay in patients with esophageal cancer undergoing surgery. There is a

reduction in post-operative complications leading to decrease in duration of hospital stay but this is not found to be of statistical significance. Thus there is a need for larger randomised control trials to further ascertain the beneficial effect of peri-operative glutamine administration in this group of patients.

CONCLUSION

Peri-operative Immunonutrition may be considered safe and effective in reducing the total length of hospital stay in patients with esophageal carcinoma undergoing elective esophagectomy as compared to standard nutrition. However, large randomized control trials are required to further prove the efficacy of glutamine in patients with esophageal carcinoma undergoing elective surgery.

There is also a need for additional studies to know about the disease specific mechanism of action of glutamine which will help in reducing secondary complications related to the operation.

There is a need for clinicians, surgeons and nutritionist to work in close coordination to develop immunonutrition into a potentially useful therapeutic intervention towards improvement of clinical outcome in patients diagnosed to have esophageal carcinoma, undergoing surgery.

LIMITATIONS

1. The sample size was small and the subjects were not randomised and hence there were many inherent biases in this study. There is a need for larger randomised trials to further ascertain the beneficial effects of glutamine.

2. Most of the studies done earlier on the use of glutamine as a single immunonutrient in patients with esophageal cancer have had small sample sizes with inherent biases and hence they were not perfect for comparison.

3. Moreover, as the years have passed, the technique of operation as well as surgeon's skill in performing esophagectomies have improved which could also have led to improved post-operative outcomes.

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ANNEXURES

CONSENT FORM

Study Title: PERIOPERATIVE IMMUNONUTRITION IN PATIENTS WITH ESOPHAGEAL CARCINOMA UNDERGOING SURGERY.

Study Number:

Subject's Name: _____

Date of Birth / Age: _____

(i) I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions. [ ]

(ii) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. [ ]

(iii) I understand that the Principal Investigator, Guide and the co-investigators, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published. [ ]

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s). [ ]

(v) I agree to take part in the above study. [ ]

Signature (or Thumb impression) of the Subject/Legally Acceptable

Date: _____/_____/_____

Name of Subject: Name of the Investigator:

Signature of Subject: Signature of Investigator:

Name of Witness/Signature of Witness:

Address of the Witness

INFORMATION SHEET

(ROLE OF PERIOPERATIVE IMMUNONUTRITION IN PATIENTS WITH ESOPHAGEAL CARCINOMA UNDERGOING SURGERY)

The following is to inform you about the above study and invite you to be a part of this study. This information sheet will give you the basic information about the proposed study. Your participation in this study is voluntary and you are free to withdraw from this study at any time during the course of your treatment. Your withdrawal will not affect the treatment or compromise the level of care you receive from Christian Medical College and Hospital, Vellore.

Purpose of the study

Human beings have an inherent immune system which provides them with protection against infections and injuries. In case of major surgeries and cancer, there is depression of this system which can lead to adverse outcomes. Immunonutrition is the addition of nutrients to normal diet which help to improve the immune system. This study is designed to observe whether the addition of these immune enhancing nutrients to the diet improves the outcome of the patients with esophageal carcinoma undergoing surgery.

Methods to be followed

If you consent to participate in this study, you will be provided with Glutamine sachets and advised regarding the method of taking this immune enhancing nutritional supplement. You will be required to take these immune enhancing nutrition supplements four days before your scheduled date of surgery and this will be continued two weeks after surgery. All the details regarding your disease and the investigations that were done will be collected from your case sheets.

Approximate duration of study

November 2014 to October 2016.

Expected cost

These supplements will be given to you free of cost.

Adverse Effects

Glutamine has no significant side effects in patients with normal liver function.

Compensation in case of study related injuries

We do not expect any injury related to this study.

Anticipated benefits from this study

There are no monetary benefits for patients participating in this study. You **MAY** have a shorter length of hospital stay and lesser incidence of post-operative complications.

What happens if you choose to withdraw from study participation?

There will be no change to the treatment or the care you are given if you withdraw from the study.

For any further queries kindly contact:

Sourav Manoram Sahu

PG Registrar

General Surgery Unit III

Paul Brand Building

Christian Medical College, Vellore

Mob: 8940276181

DATASHEET

ID	NAME	AGE	SEX	Ht.	Wt.	BMI	Hb	TLC	N%	L%	SA	IMN	DHS	PNEU	WI	AL
1	MD. AYUB ALI	49	1	157	35	14.2	11	10800	73	17	2.5	1	12	2	1	2
2	KAMALUDDIN	62	1	160	48	18.8	11	6800	70	13	3.4	1	12	2	2	2
3	MOHAMMAD SHAH ALAM	56	1	154	57	24	12	7600	42	45	3.5	1	13	2	2	2
4	DEBASHIS SARKAR	53	1	167	70	25.1	11	7100	55	35	3.7	1	11	1	2	2
5	MUHAMMAD	65	1	160	45	17.6	10	13100	83	11	2.8	1	10	2	2	2
6	RISHANIAKI WANKHAR	48	1	158	55	22	12	6900	66	20	4	1	10	2	2	2
7	SAMATHA K.	37	2	152	71	30.7	11	16800	90	7	4.5	1	13	1	2	2
8	SHABIA KHATUN	63	2	155	60	25	11	6500	76	11	4.2	1	19	2	2	2
9	BEGUM JAHN ARA	61	2	150	53	23.6	11	4300	58	41	4	1	8	2	2	2
10	MD. FAZAR ALI	66	1	150	56	24.9	11	6700	54	18	3.7	1	13	2	2	2
11	SAHADEO SINGH BISWAKARMA	64	1	176	64	20.7	12	7000	60	21	4	1	13	2	2	2
12	ERWISLINA LYNGDOH	59	2	146	40	18.8	10	6400	62	24	3.3	1	19	2	2	2
13	SANJAY KUMAR SAHU	46	1	163	71	26.7	14	4900	71	13	4.4	1	10	2	2	2
14	S.K MOHAMMAD FARUK HOSSAIN	43	1	160	51	19.91	12	7900	60	21	4.5	1	13	2	2	2
15	NAGENDRANATH RABIDAS	67	1	169	53	18.6	13	14400	54	31	4.4	1	12	2	2	2
16	JOHN P.T	57	1	160	58	22.7	12	6000	53	29	4.4	1	21	2	2	2
17	KAZI MOMTAZ BEGUM	62	2	144	54	26	13	6000	62	28	4.4	1	18	2	2	2
18	TAJMUL ANSARI	57	1	166	60	21.8	14	5500	34	46	4.2	1	18	2	2	1
19	MIHIR KUMAR MAJEE	57	1	165	60	22	10	12000	62	28	3	1	12	2	2	2
20	BHOLA SAHU	59	1	165	55	20.2	9	7300	71	14	3.6	1	8	2	2	2
21	PRADEEP KUMAR GUPTA	44	1	165	48	17.6	10	7500	60	24	4.2	1	12	2	2	2
22	BATAILIN WANKHAR	40	2	151	39	17.1	11	3100	48	23	3.6	2	19	2	2	2
23	MEDALIN NONGRUM	56	2	152	52	22.3	14	4900	64	22	4.4	2	42	2	2	2
24	MOHAN CHANDRA BORAH	56	1	173	64	21.4	12	10800	46	27	4.5	2	13	2	2	2
25	MORTON KHARBULI	49	1	152	41	17.7	13	3800	51	31	4	2	11	2	2	1
26	TAKO YEKAR	65	1	171	67	22.9	13	6400	40	42	4.1	2	11	2	2	2
27	PARIMAMAL S.	38	2	152	54	23.4	11	8300	56	14	3.7	2	15	2	1	2
28	ANNAMMA SAMUEL	65	2	153	57	24.3	9	3500	69	23	4.5	2	14	2	2	2
29	SRNIVASAN V.	51	1	165	61	22.4	14	6700	79	5	3.7	2	16	2	2	1
30	THANGAVELU	57	1	165	89	32.7	12	7000	48	37	4.1	2	14	2	2	2
31	MOHAMMAD IBRAHIM MASUD	49	1	162	51	19.4	13	10900	32	33	3.8	2	16	2	2	1
32	SUBASH CHANDRA	64	1	150	53	23.6	11	7200	62	28	3.8	2	15	2	2	2

33	RINA MUTSUDDY	63	2	153	45	19.2	11	8100	61	18	2.5	2	18	1	2	2
34	MURALI G.	46	1	172	62	21	13	3300	77	12	3.9	2	15	2	2	2
35	MAHENDRA MANDAL	53	1	175	50	16.3	14	5600	48	36	4.6	2	22	1	2	2
36	NICHAL SUTNGA	60	1	160	48	18.8	13	6500	60	20	3.9	2	22	1	2	2
37	JAYANANDA DAS	52	1	170	50	17.3	12	6000	59	18	3.8	2	12	1	2	2
	PALATHINGAL	66	1	170	74	25.6	13	7800	60	30	4.3	2	31	2	2	2
38	JOSEPH EPHREM															
39	BAGAN CHANDRA DAS	63	1	160	44	17.2	11	7200	62	14	3.9	2	13	1	2	2
40	LALVENGLIEN RALSAN	50	1	163	68	25.6	13	6200	71	14	4.4	2	44	1	2	2
41	SATISH NARAYAN	40	1	179	64	20	12	7100	63	28	3.6	2	30	2	2	2
42	SANTOSH MINJ	57	1	176	60	19.4	14	9000	69	12	4	2	21	1	2	1
43	HARAN BISWAS	33	1	170	52	18	13	13700	53	30	4.4	2	12	2	2	2